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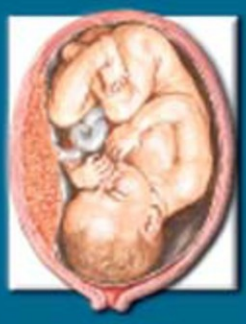

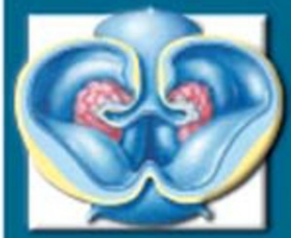

Netter's Atlas of Human Embryology

Larry R. Cochard

Updated Edition

F. Netter M.D.

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NETTER'S ATLAS OF HUMAN EMBRYOLOGY, Updated Edition

ISBN: 978-1-4557-3977-6
eBook ISBN: 978-1-4557-3978-3
Library of Congress Catalog No: 2001132799

Printed in the United States of America
First Printing, 2002

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To Dr. David Langebartel

As my teacher and mentor at the University of Wisconsin—Madison,
he stressed the relationship between embryology and adult anatomy,
and he did so with energy, authority, and a considerable amount of humor.

And to the memory of

Dr. Leslie B. Arey

He was a colleague at the beginning of my career at Northwestern.
It was a privilege and a very humbling experience
for a young, green anatomist to teach with the
20th-century master of embryology, anatomy, and histology.

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Preface

This book is intended for first-year medical students, dental students, and other beginning students of embryology. As an atlas, it is a showcase for the incomparable artwork of Dr. Frank H. Netter. The Netter paintings in this *Atlas* were published in *The Netter Collection of Medical Illustrations,* Dr. Netter's series of systemic monographs that integrate anatomy, embryology, physiology, pathology, functional anatomy, and clinical anatomy. They were also published in the *Clinical Symposia* that address particular topics. As necessary, new images were created by John A. Craig, MD, and Carlos Machado, MD. Plates were selected to match the scope of material that is suitable for beginning students and arranged in a logical sequence.

The theme throughout this book is an emphasis on morphological patterns in the embryo and how they relate to the organization and function of structures in the adult. Another important focus is the embryological basis of congenital birth defects. Descriptive embryology can be an educational goal, but the study of embryology is more effective, rewarding, and relevant when it is placed in a biological or clinical context that goes beyond the embryo itself. The focus on morphological themes in prenatal development makes it easier to learn adult anatomy and to understand an abnormality in a patient. In keeping with this idea, this *Atlas* contains some Netter plates of adult anatomy. These include parts of the body where complex anatomy has embryonic relevance. They also provide context to help show the relationships between primordia and derivatives.

Like anatomy, embryology is a very visual subject that lends itself to an atlas format. Embryological pictures can also be difficult and frustrating for students because of the three-dimensional complexity of the embryo and the unfamiliar structures and relationships. To address this problem, the book consists of more than just labeled images. It contains tables, schematics, concepts, descriptive captions, summaries, chapter glossaries, and concise text at the bottom of each page that address all of the major events and processes of normal and abnormal development. Histological principles are briefly covered to help the uninitiated understand the many references to embryonic tissues in this book.

Little was known about the genetic and molecular basis of development when Dr. Netter drew most of his illustrations, and an atlas is not the ideal medium to convey this type of information. I believe it is important, though, to introduce the subject and to include examples of the control of development. Illustrations from the *Atlas* are used to introduce cellular, molecular, and genetic concepts such as induction, apoptosis, growth factors, and genetic patterning and determination. These are by necessity selective and include major events (e.g., limb development, segmentation of the head) or processes that have broad significance in development (e.g., the interactions between epithelia and connective tissue in organ development). If nothing else, this material will serve to remind students of the complexity of development and the dynamic events at the cellular and molecular level.

The terminology tables at the end of each chapter are also selective. The terms include major structures, potentially confusing structures, and histological or anatomical terms that provide context. The glossary is also an opportunity to include

terms that did not make it into a chapter or to elaborate on important ones. At the risk of some overlap, I decided to have a terminology section at the end of each chapter instead of at the end of the book. This makes it a more effective learning tool, as students use this *Atlas* in their studies rather than an isolated reference feature.

Chapter 1 is an overview of the major developmental periods, events, and processes and ends with a section on the mechanisms of abnormal development and the classification of anomalies. Chapter 2 addresses gastrulation, the vertebrate body plan, and the placenta. Chapters 3 through 8 are organized by systems and include congenital defects. Chapter 9 is on the head and neck region.

This annotated *Atlas* can serve as a bridge between the material presented in the classroom and the detail found in textbooks. It can be useful for board exam review, and to that end, there is an appendix that summarizes all of the major congenital anomalies and their embryonic basis. More than anything, this *Atlas* is about the art of Dr. Netter. The clarity, realism, and beauty of his illustrations make the study of embryology more enlightening and enjoyable.

Larry R. Cochard, PhD

Frank H. Netter, MD

Frank H. Netter was born in 1906 in New York City. He studied art at the Art Student's League and the National Academy of Design before entering medical school at New York University, where he received his medical degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

Icon Learning Systems acquired the Netter Collection in July 2000 and continues to update Dr. Netter's original paintings and to add newly commissioned paintings by artists trained in the style of Dr. Netter.

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book Netter Collection of Medical Illustrations, *which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published.* The Netter Atlas of Human Anatomy, *first published in 1989, presents the anatomical paintings from the Netter Collection. Now translated into 11 languages, it is the anatomy atlas of choice among medical and health professions students the world over.*

The Netter illustrations are appreciated not only for their aesthetic qualities, but more important, for their intellectual content. As Dr. Netter wrote in 1949, "… clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration *if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what make them so intellectually valuable.*

Frank H. Netter, MD, physician and artist, died in 1991.

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About the Author

Larry R. Cochard, PhD, is Associate Professor of Medical Education and Assistant Professor of Cell and Molecular Biology in the Office of Medical Education and Faculty Development at the Northwestern University Feinberg School of Medicine, where he has taught embryology, anatomy, and histology since 1982. He has won numerous "Outstanding Teacher" awards at Northwestern as one of the top five teachers selected by the combined M1 and M2 classes. He was a three-time winner of the American Medical Women's Association Gender Equity Award for teaching, and four-time winner of the George H. Joost award for M1 basic science teacher of the year. He is a biological anthropologist with research interests in the development and evolution of the primate skull.

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Acknowledgments

Many people made my job easier and made this a better book. I thank the following faculty members and students here at the Feinberg School of Medicine for their helpful comments, edits, and/or answers to a continuous string of questions: Dr. Bob Berry, Dr. Joel Charrow, Jeff Craft, Dr. Marian Dagosto, Aaron Hogue, Najeeb Khan, Dr. Jim Kramer, Kelly Ormond, Dr. Randy Perkins, Dr. Matt Ravosa, Dr. Brian Shea, Dr. Al Telser, and Dr. Jay Thomas. I also wish to thank the reviewers, for helping to shape the book and to bring some new developments to my attention. The reviewers were:

Wojciech Pawlina, MD
Mayo School of Medicine

Thomas A. Marino, PhD
Temple University School of Medicine

Daniel O. Graney, PhD
University of Washington
School of Medicine

Leslie Gartner, PhD
University of Maryland Dental School

Bruce Carlson, MD, PhD
University of Michigan

Andreas H. Weiglein, MD
Karl-Franzens-University
Graz, Austria

Ronald W. Dudek, PhD
Brody School of Medicine
East Carolina University

I assume full responsibility for any errors or inaccuracies that may remain.

The *Atlas* has new illustrations by John Craig, MD, and Carlos Machado, MD, on the few topics Dr. Netter did not address and for some learning tools I thought might be helpful. That their plates blend so well in the book is a tribute to their skill. I am grateful for their contribution.

I greatly appreciate the work and support of my editors and the entire team at Icon Learning Systems. I thank executive editor Paul Kelly for a phone call I received as I just arrived at my office on January 2, 2001, in which he said, "How about doing a Netter atlas of embryology?" I am grateful to developmental editor Kate Kelly for taking my grandiose and rambling vision of the book and making it a more focused, relevant, and useful account that is the embryology I actually teach. A special thanks goes to managing editor Jennifer Surich for her skill and good humor in solving problems and her ability to decipher my often-obscure instructions. I also thank Suzanne Kastner and the staff at Graphic World, Inc., for their excellent work in the display of the Netter art on the page and with the difficult graphic adjustments that needed to be made in this *Atlas*.

The most important contributor to the book was my wife, Sue. The project was so much easier because of her support, patience, and encouragement, and for that she has my profound gratitude.

Last but not least I thank my students, past and present, for their perceptive questions about embryology that have made me a better teacher. I also thank them for putting up with my insistence that the secret to understanding the embryo is understanding the difference between somatopleure and splanchnopleure!

Larry R. Cochard, PhD

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CHAPTER 1

AN OVERVIEW OF DEVELOPMENTAL EVENTS, PROCESSES, AND ABNORMALITIES

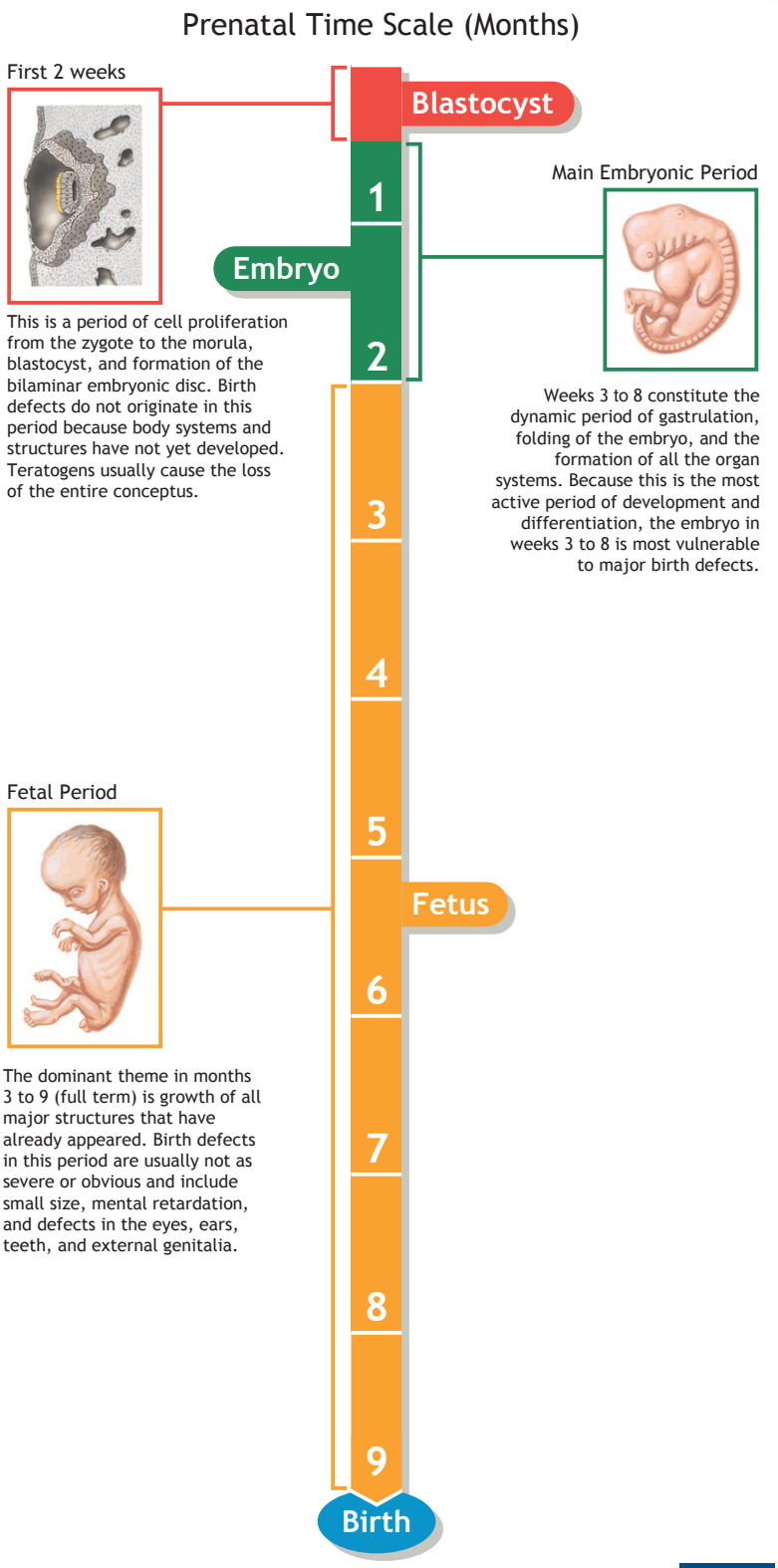
PRIMORDIUM

The zygote is the beginning of human development.

OVERVIEW

Prenatal development can be divided into a period of cell division (weeks 1 and 2 after fertilization), an embryonic period (weeks 2 through 8), and a fetal period (weeks 9 through 38). In the first 2 weeks after fertilization, a blastocyst develops and sinks into the mucosal lining of the uterus during implantation. It consists of a two-layered embryonic disc of cells and three membranes that are external to it (trophoblast/chorion, amnion, and yolk sac). Most of the organ systems develop in the main embryonic period through week 8, and the embryo assumes a human appearance. The fetal period occupies the last 7 months. It is a period of growth and elaboration of organs that are already present. Three categories of genes (maternal, segmentation, and homeotic) establish patterns and tissue fates in the embryo, and dynamic interactions between cells characterize the differentiation and development of organs. Abnormal development can be classified by the cause (e.g., genetic versus environmental), by the nature of the effect on a structure or tissue, by the relationship between defects, and by their severity.

TIMELINE



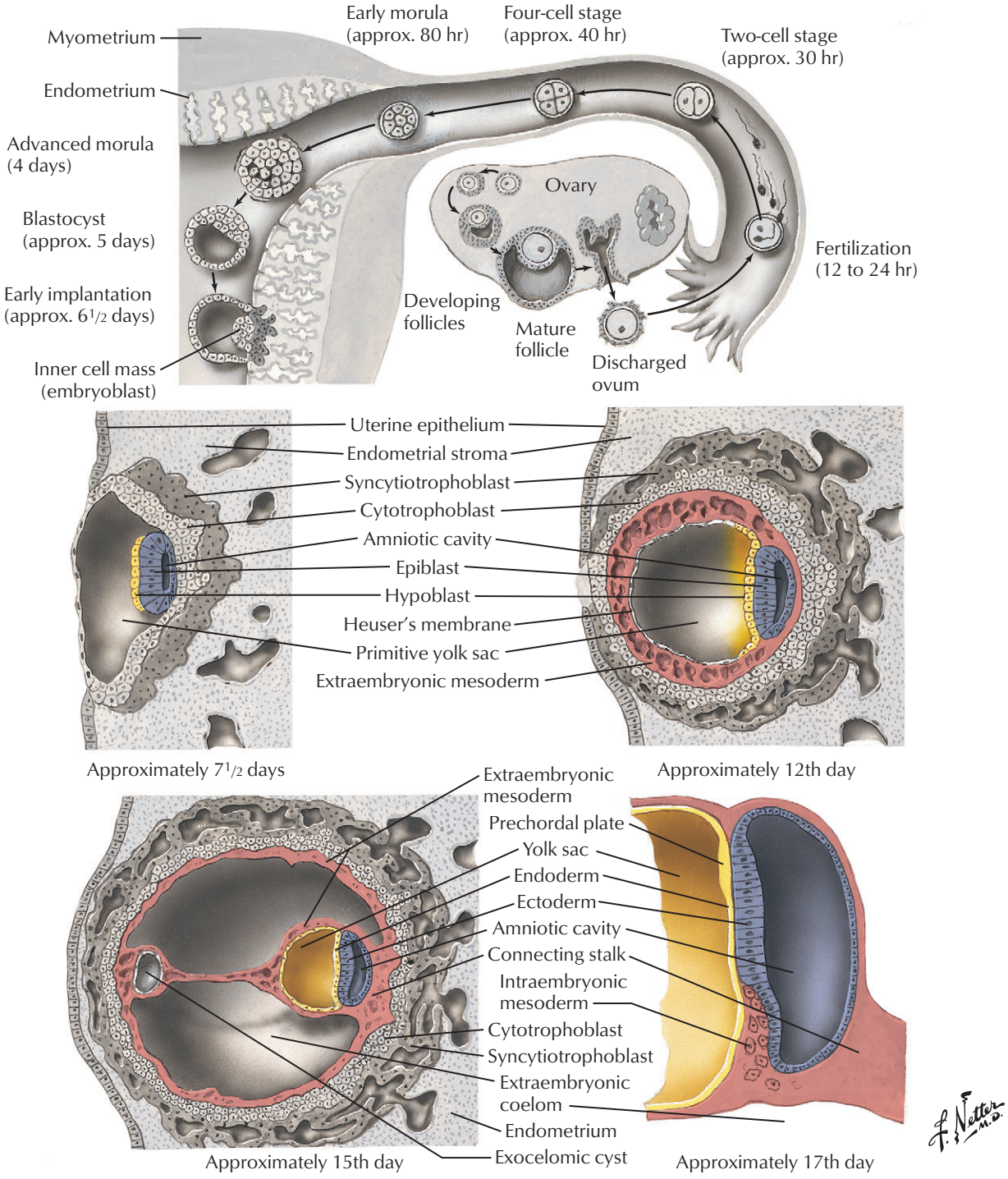


FIGURE 1.1 THE FIRST AND SECOND WEEKS

Cell division and the elaboration of structures that will be outside the embryo (extraembryonic) characterize the first 2 weeks. The **morula,** a ball of cells, becomes hollow to form a **blastocyst** that develops into a placenta and membranes that will surround the future embryo. The embryo is first identifiable as a mass of cells within the blastocyst late in the first week. By the end of week 2, the embryo will be a disc two cell layers thick. The **conceptus** (all of the intraembryonic and extraembryonic products of fertilization) takes most of week 1 to travel down the uterine tubes to the uterine cavity. In week 2, the blastocyst sinks within the endometrial wall of the uterus (implantation).

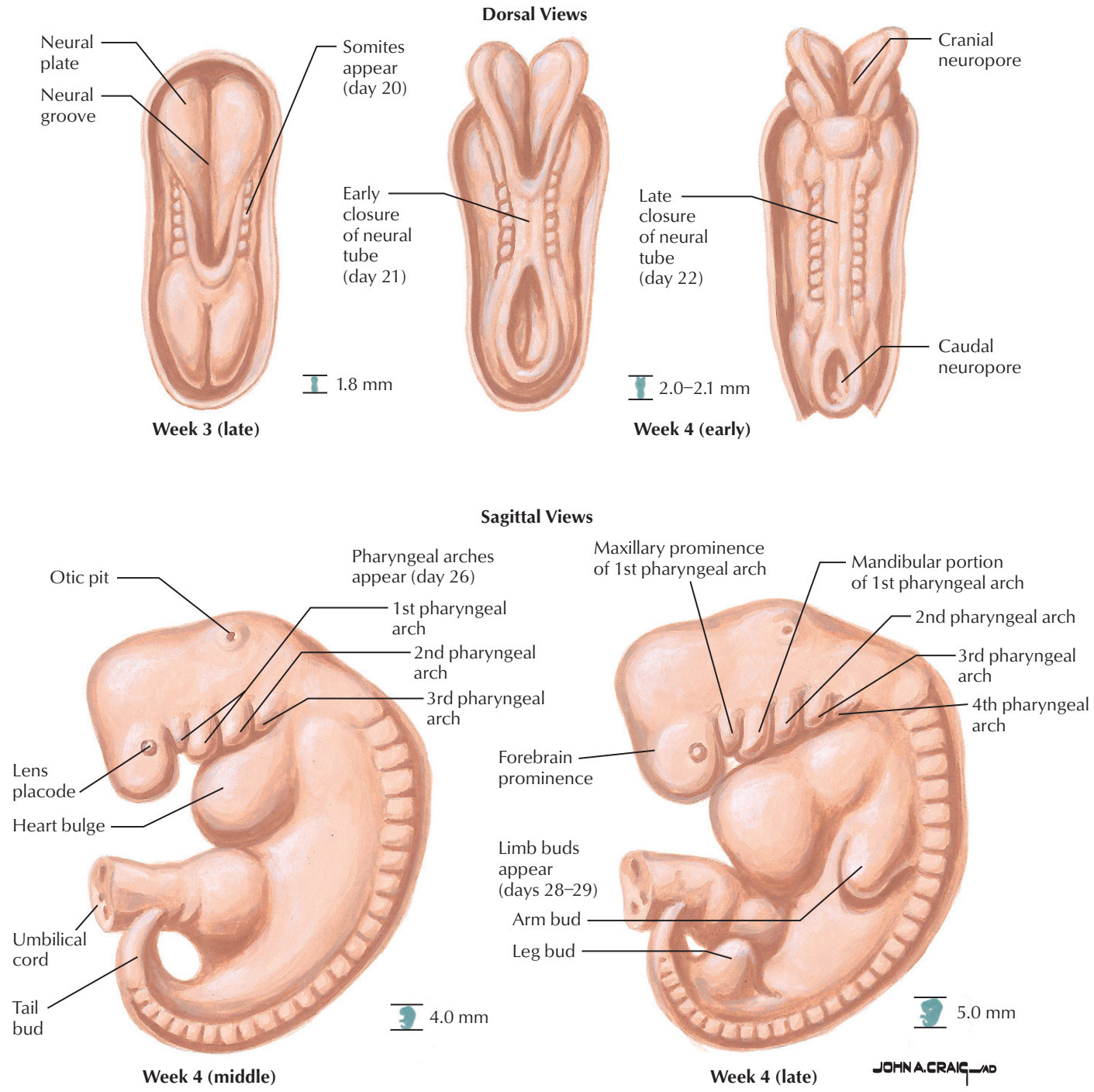


FIGURE 1.2 THE EARLY EMBRYONIC PERIOD

The embryonic period (weeks 3 through 8) begins with gastrulation in the bilaminar disc and ends with an embryo that looks very human. The embryonic disc folds into a cylinder to establish the basic characteristics of the vertebrate body plan, and the primordia of all the organ systems develop. It is a very dynamic period of differentiation, development, and morphological change. The cardiovascular system is the first organ system to function (day 21/22) as the embryo becomes too large for diffusion to address the metabolic needs of the embryonic tissues.

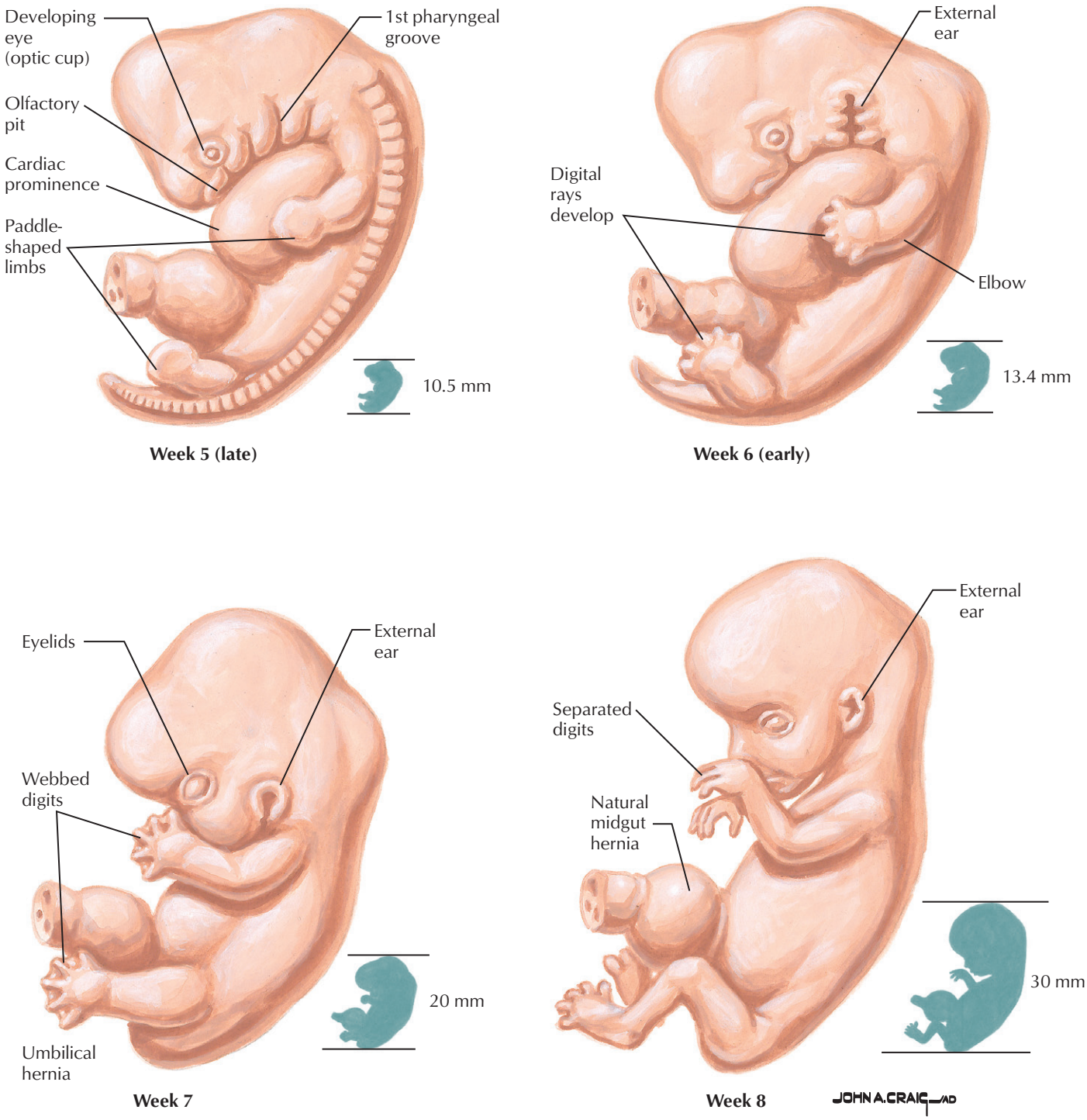


FIGURE 1.3 THE LATE EMBRYONIC PERIOD

In the second half of the embryonic period, the human appearance of the embryo emerges. The neuropores have closed, the segmentation of the somites is no longer visible, and the pharyngeal arches are blending into a human-looking head. The upper and lower extremities are extending from the body, and fingers and toes develop. Eyes, ears, and a nose are visible, and the embryonic tail disappears with relative growth of the trunk.

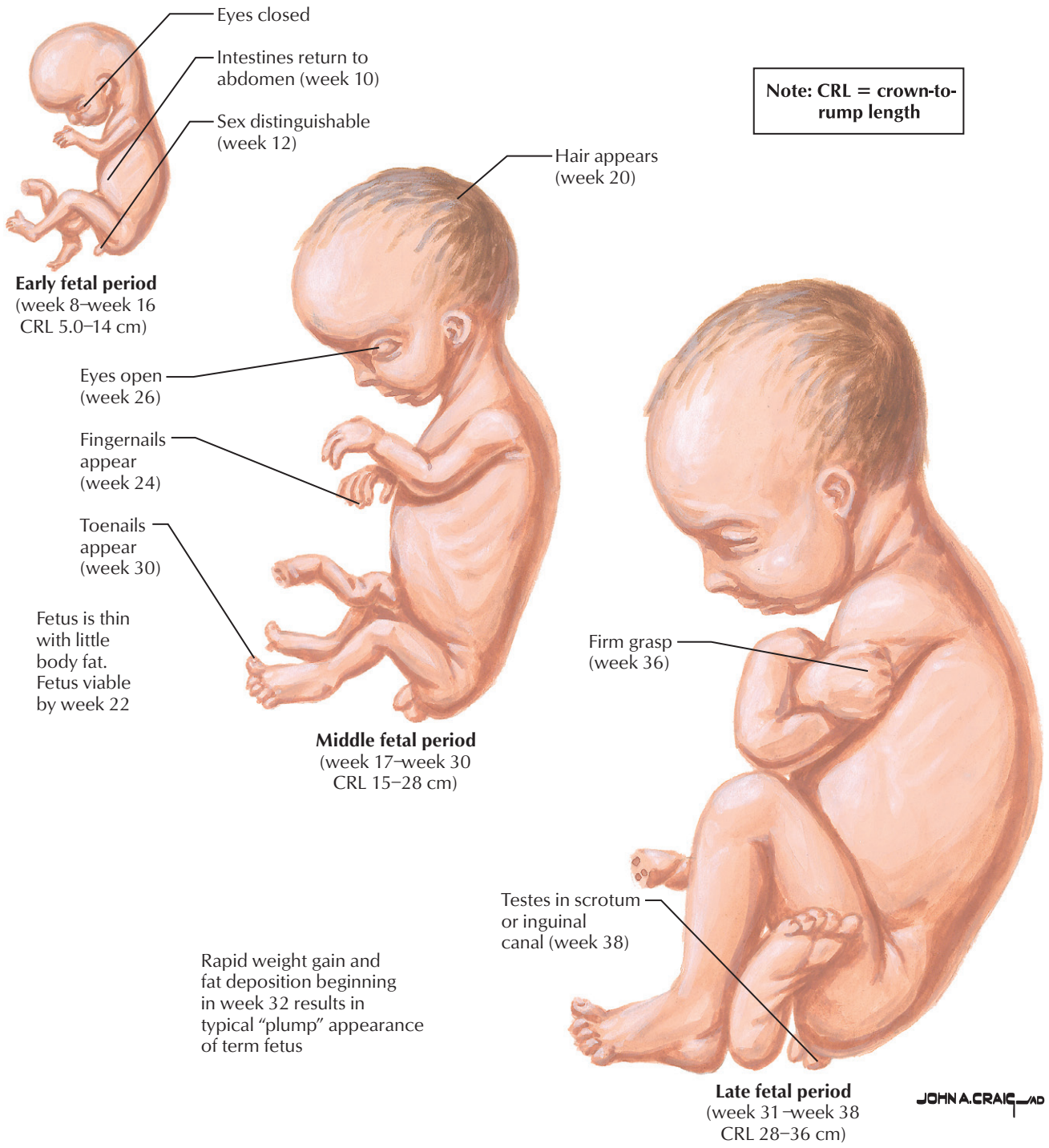


FIGURE 1.4 THE FETAL PERIOD

The theme of the 7-month fetal period is the growth and elaboration of structures already present. Movement of the fetus within the amniotic fluid is a crucial part of the process. The fluid is maternal tissue fluid that crosses the chorion and amnion. It is increasingly supplemented by fetal urine, which is more similar to blood plasma than urine because metabolic waste products in the blood are eliminated in the placenta. The fetus swallows up to 400 mL of amniotic fluid each day for the normal development of oral and facial structures and to provide a favorable environment for the development of the epithelia lining the airway and gastrointestinal tract. The fluid is absorbed into fetal tissues via the latter.

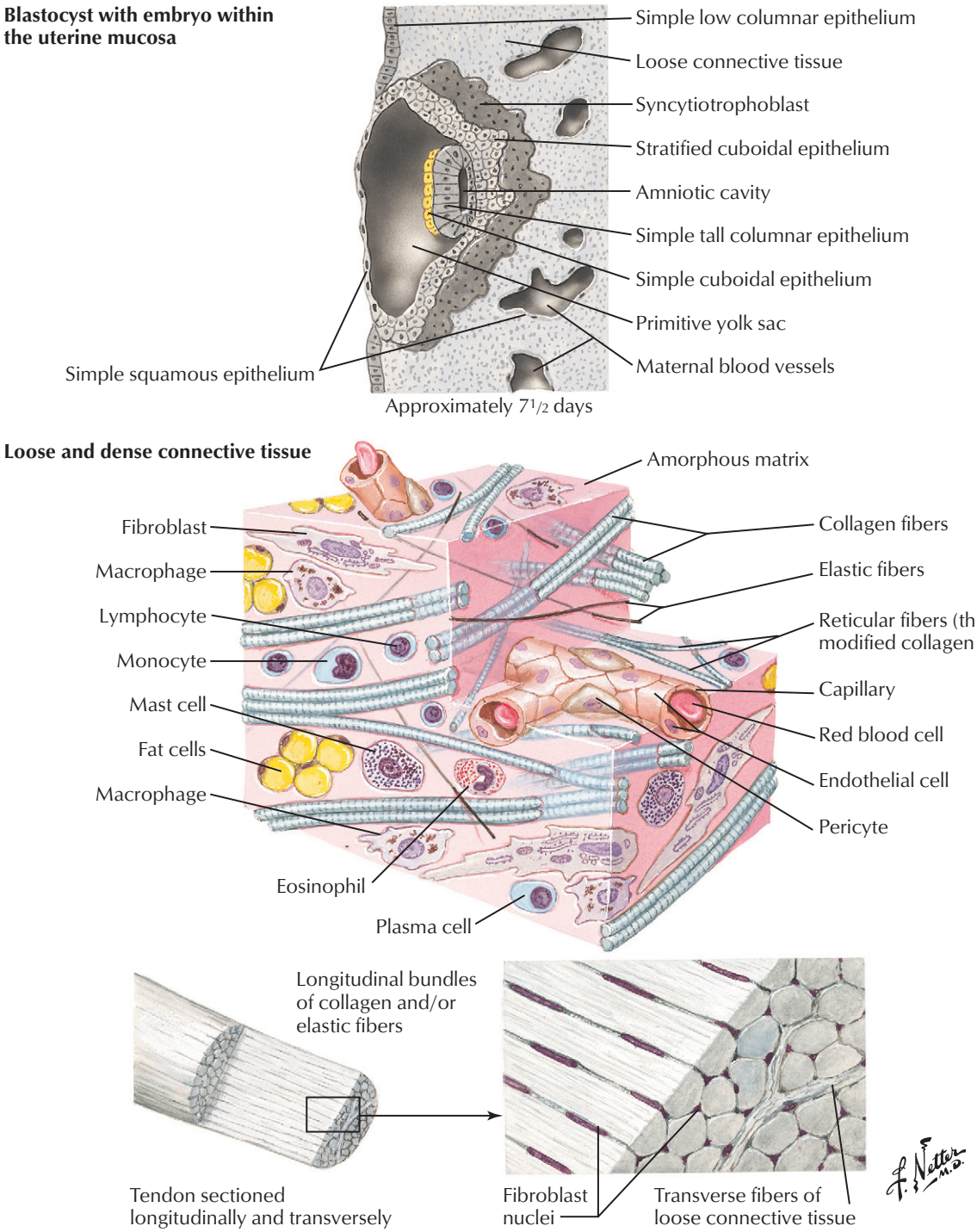


FIGURE 1.5 SAMPLES OF EPITHELIA AND CONNECTIVE TISSUE

Histology is the microscopic study of cells, tissues, and organs. Every tissue in the body is classified as nerve, muscle, epithelium, or connective tissue. Epithelia line body surfaces and have cells in tight contact with each other. Epithelia are classified as simple (one cell layer thick) or stratified and according to the shape of the cells on the surface (e.g., squamous [flat], cuboidal, columnar). Connective tissue cells are dispersed in some type of extracellular matrix. **Dense connective tissue** is dense with fibers and contains a higher ratio of matrix to **fibroblasts,** the cells that secrete and maintain the matrix. **Loose connective tissue** has relatively more cells than dense connective tissue and a greater variety of fibers, cells, and matrix molecules.

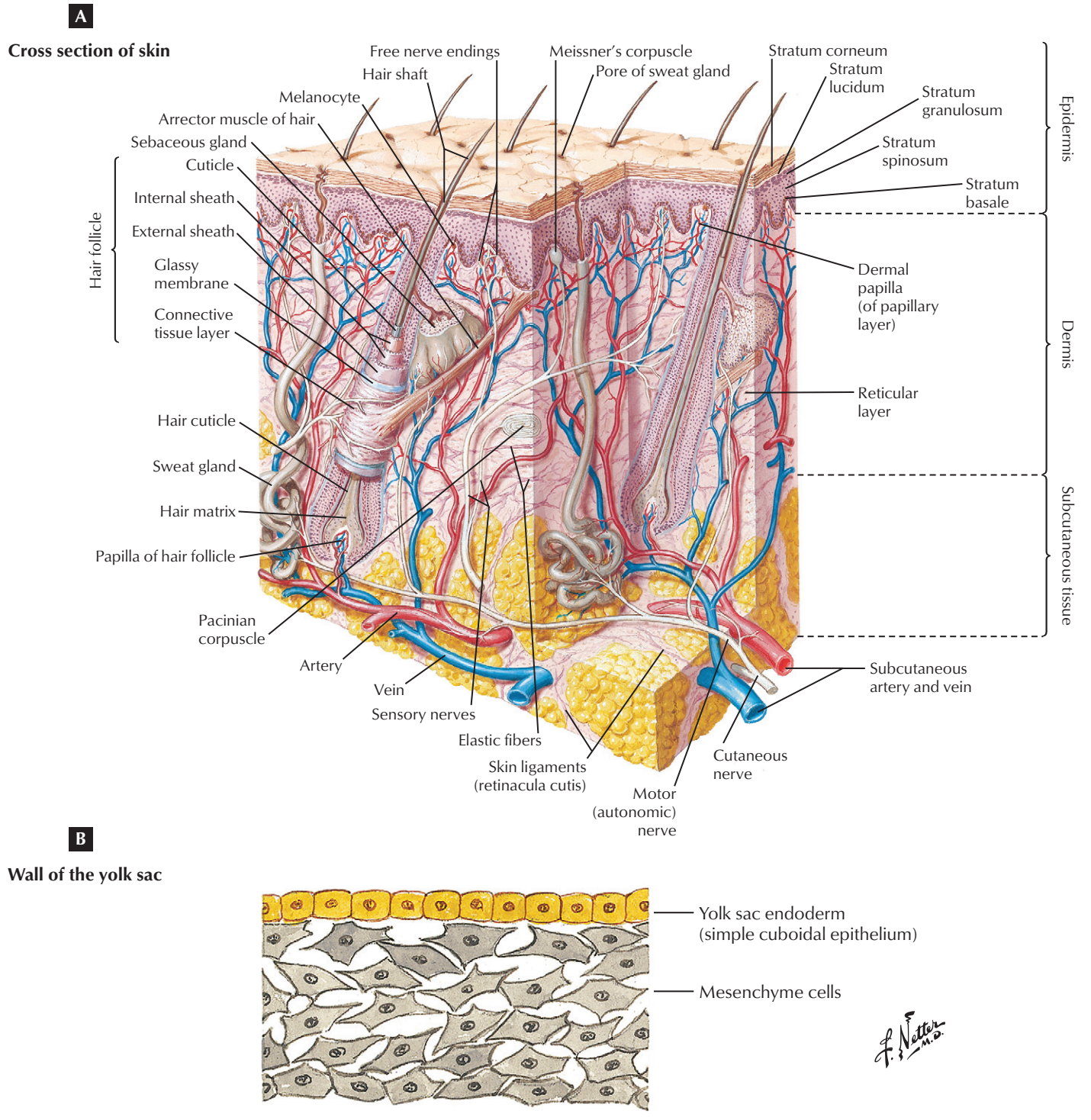
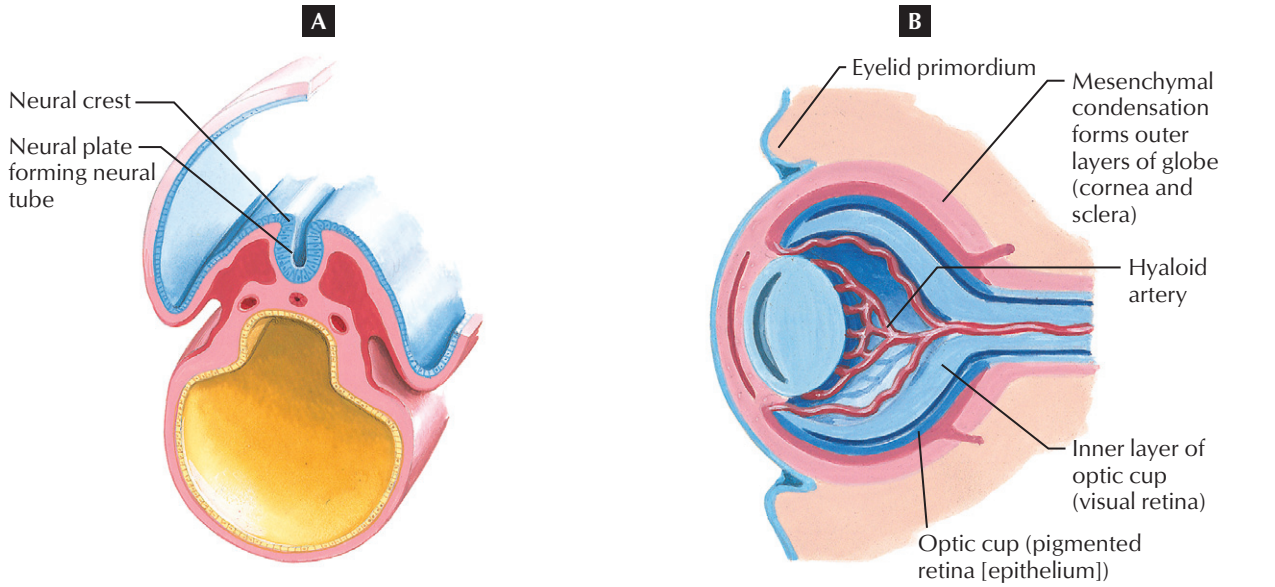


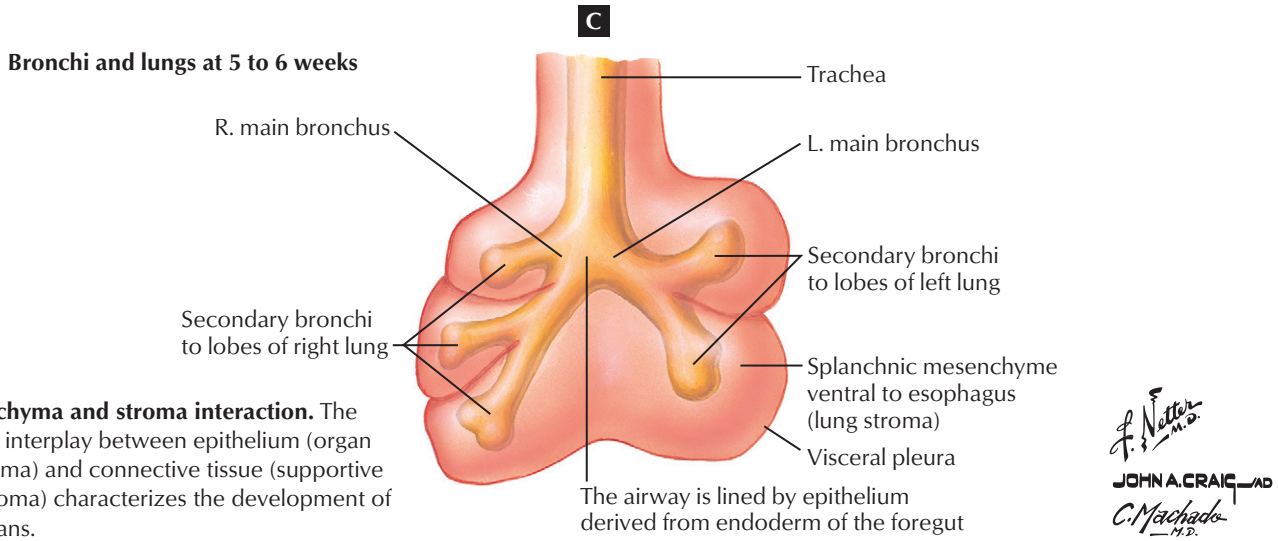
FIGURE 1.6 SKIN AND EMBRYONIC CONNECTIVE TISSUE

The epidermis of skin is a stratified, squamous epithelium with a protective, keratinized layer of dead cells on the surface. The dermis is dense, irregular connective tissue where the collagen fibers are arranged in "irregular" bundles. The fascia below the skin (subcutaneous) is loose connective tissue with a high fat content. The epidermis develops from the surface ectoderm of the embryo; the connective tissue layers are derived from loose, undifferentiated embryonic connective tissue called mesenchyme (demonstrated in B, the wall of the yolk sac). Mesenchyme is a very cellular connective tissue with stellate-shaped cells.

A. Neurulation. The classic and perhaps most-studied example of induction is the formation of the neural tube, where the surface ectoderm (neural plate) is induced by the notochord and paraxial columns.

B. Complex induction: eye development. The eye requires at least eight inductive interactions, most of which are specific and require the participation of both tissues in a particular role.





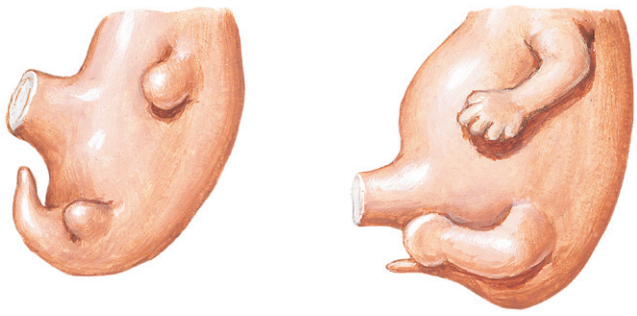
C. Parenchyma and stroma interaction. The inductive interplay between epithelium (organ parenchyma) and connective tissue (supportive organ stroma) characterizes the development of most organs.

FIGURE 1.7 INDUCTION

Induction is the interaction between two separate histological tissues or primordia in the embryo that results in morphological differentiation. One tissue usually induces the other, but one or both can participate in subsequent organogenesis. The signal varies. It may be a molecule, an extracellular matrix secreted by one of the tissues and encountered by the other, or it may require direct cellular contact between the two embryonic rudiments. Some inductions (e.g., neural tube formation) are nonspecific. A variety of factors can cause the response; the inducing tissue plays no unique role.

A

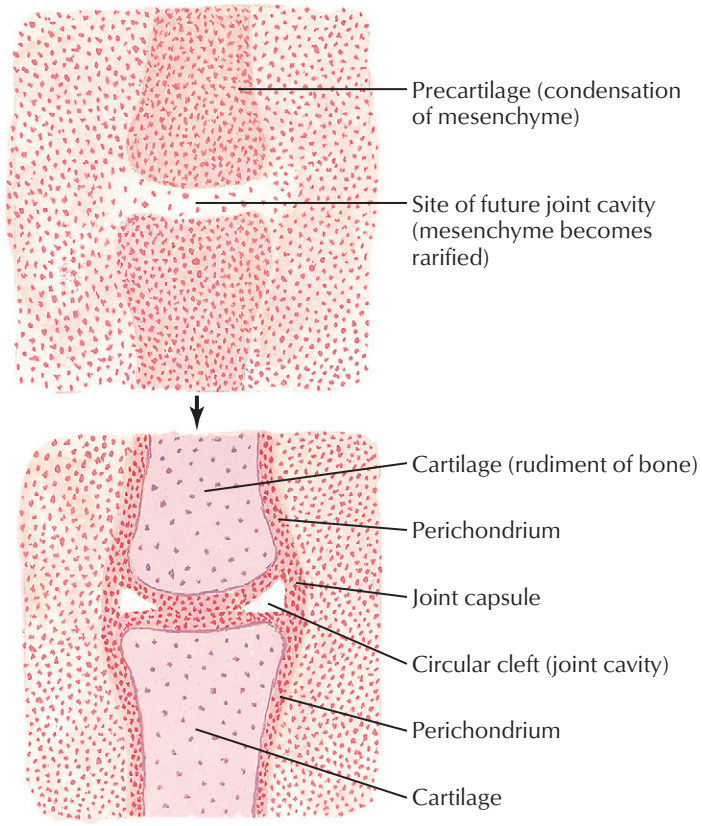
Upper and lower limb buds at 5 and 6 weeks



A. An obvious function of apoptosis is the disappearance of a large number of tissues and structures in development. Fingers and toes form by the elimination of tissue between them.

B

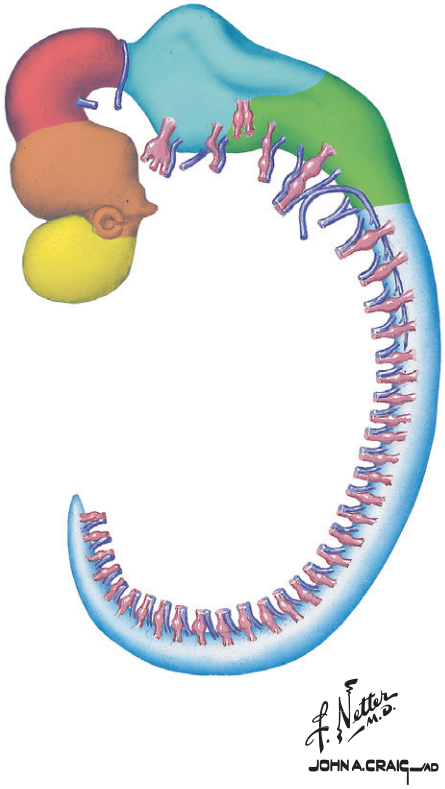
Formation of a joint cavity between two developing bones



B. Apoptosis plays an important role in cavitation and the shaping of structures. The lumen of vessels, ducts, hollow organs, and other spaces form via apoptosis.

C

Cranial and spinal nerves at 36 days



C. Another important role of apoptosis is the cell selection process that occurs in the development of most organs. This is particularly significant in the nervous system, where huge numbers of neurons die to allow for the proper connections and functions of the remaining cells.

FIGURE 1.8 APOPTOSIS

Apoptosis is programmed cell death, an extremely important process of normal development. It is initiated in mitochondria in response to a variety of stimuli. Cytochrome c and other molecules are released into the cytoplasm, triggering a cascade of reactions involving a number of cystein proteases called **caspases.** The result is the condensation of chromatin in the nucleus and the degradation of DNA. There may also be caspase-independent mechanisms for apoptosis that act in very early development.

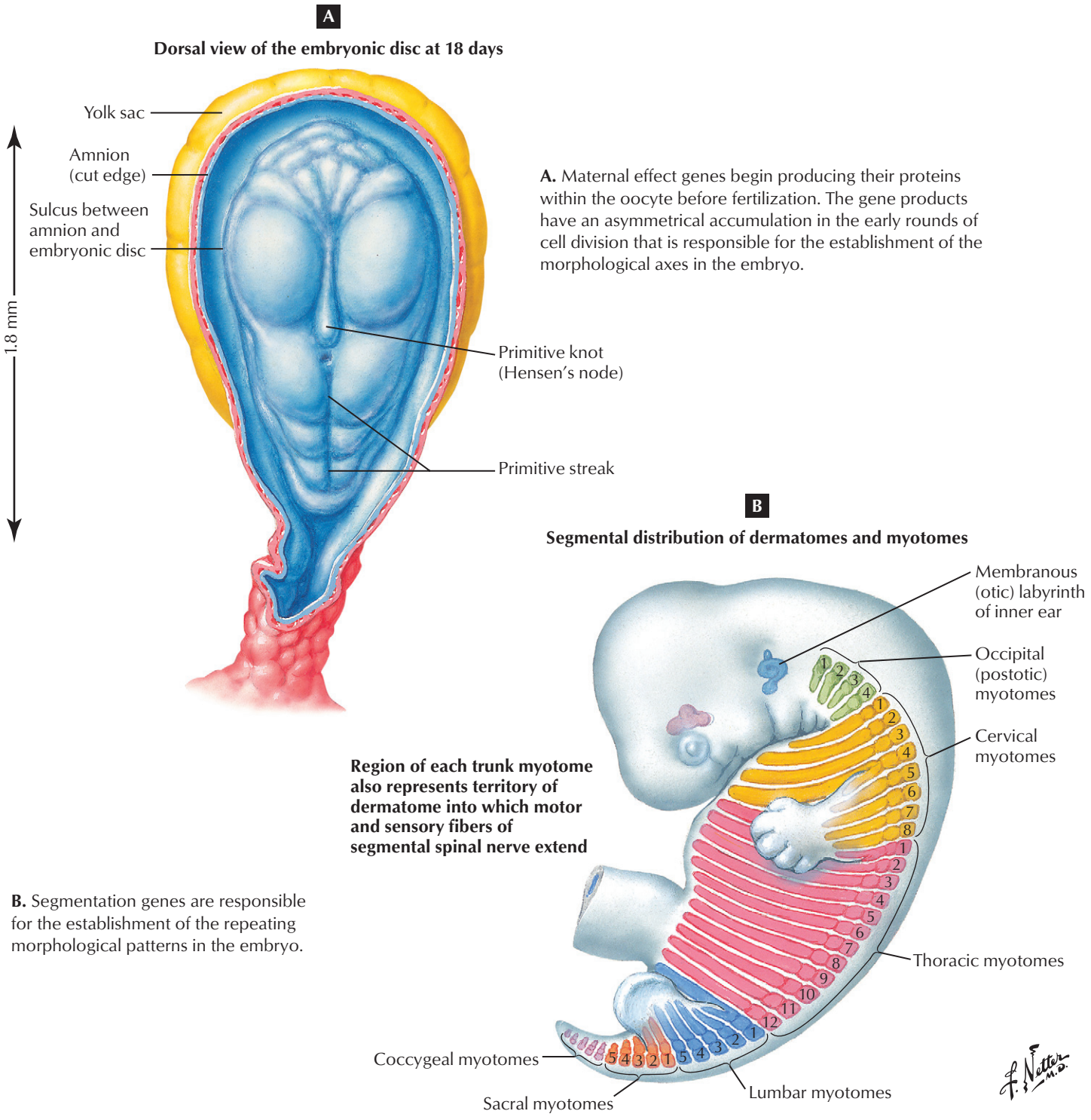
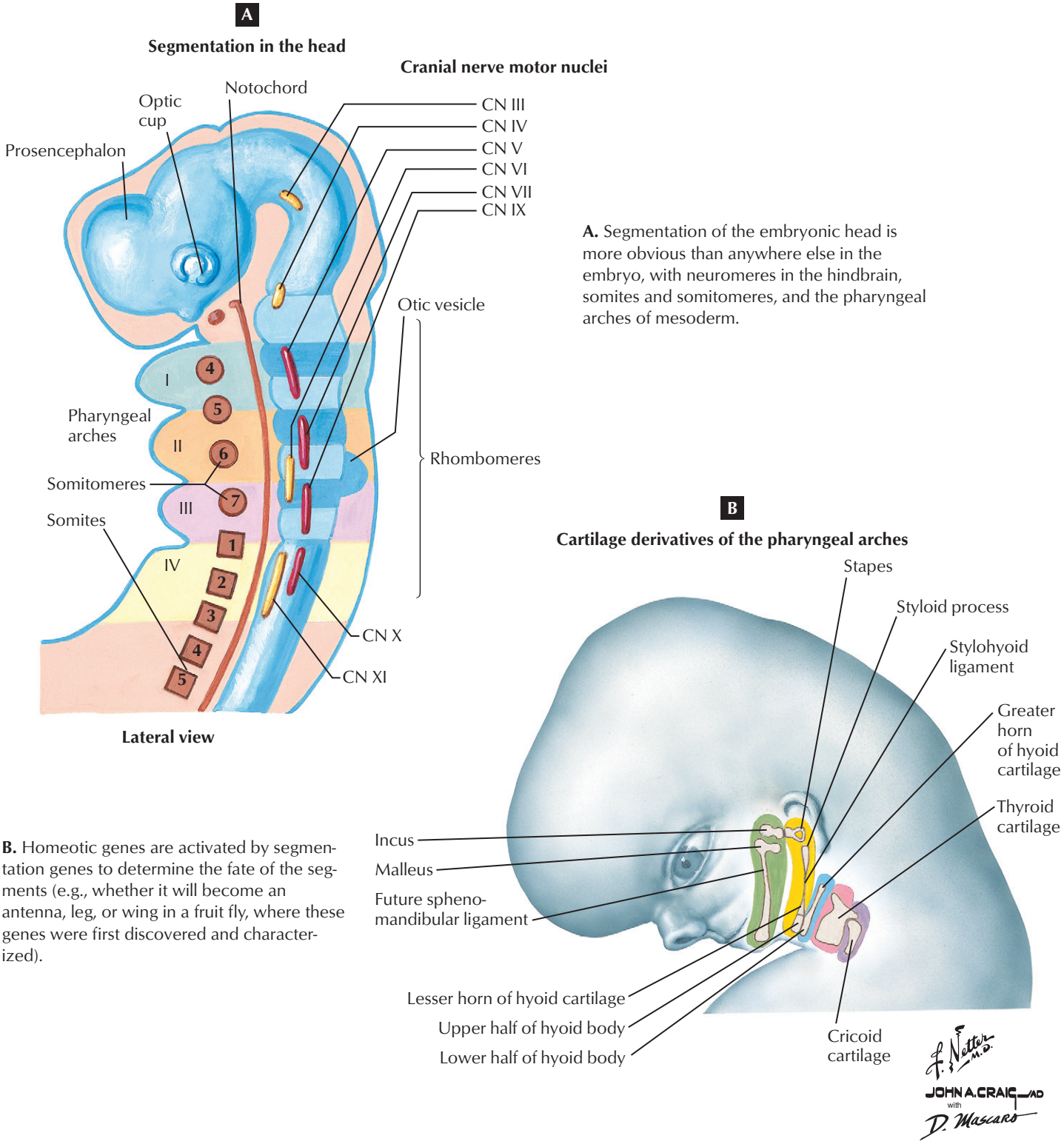


FIGURE 1.9 GENETIC DETERMINATION OF EMBRYONIC AXES AND SEGMENTS

The establishment of a bilaterally symmetrical, segmented body plan with craniocaudal and dorsoventral axes is a hallmark of chordate (and vertebrate) development. These features are the result of three gene categories: **maternal effect, segmentation,** and **homeotic genes.** Their products are mostly transcription factors that regulate the expression of other genes. Many of these genes contain a 183 base pair **homeobox,** a phylogenetically conservative segment whose product is the DNA-binding component of the transcription factor. These three gene groups act in sequence in a complex cascade involving regulatory gene interactions within each group, from one group to the next, and with structural genes.



A. Segmentation of the embryonic head is more obvious than anywhere else in the embryo, with neuromeres in the hindbrain, somites and somitomeres, and the pharyngeal arches of mesoderm.

B. Homeotic genes are activated by segmentation genes to determine the fate of the segments (e.g., whether it will become an antenna, leg, or wing in a fruit fly, where these genes were first discovered and characterized).

FIGURE 1.10 SEGMENTATION AND SEGMENT FATES

Segmentation is expressed throughout the embryo in the formation of cranial and spinal nerves, the vertebral column and ribs, early muscle development, and patterns of blood vessel formation. The pharyngeal arches of mesoderm in the embryonic head are the most externally visible segments. Segmentation genes of the *Hox* gene family (and others) play a major role in arch development, and they extend their effects to the cranial somites and segments of the hindbrain (rhombomeres). Homeotic genes are required to determine the fate of the segments. Examples shown in part B include the development of ear ossicles, hyoid bone, cartilages of the larynx, etc., from mesoderm in each pharyngeal arch.

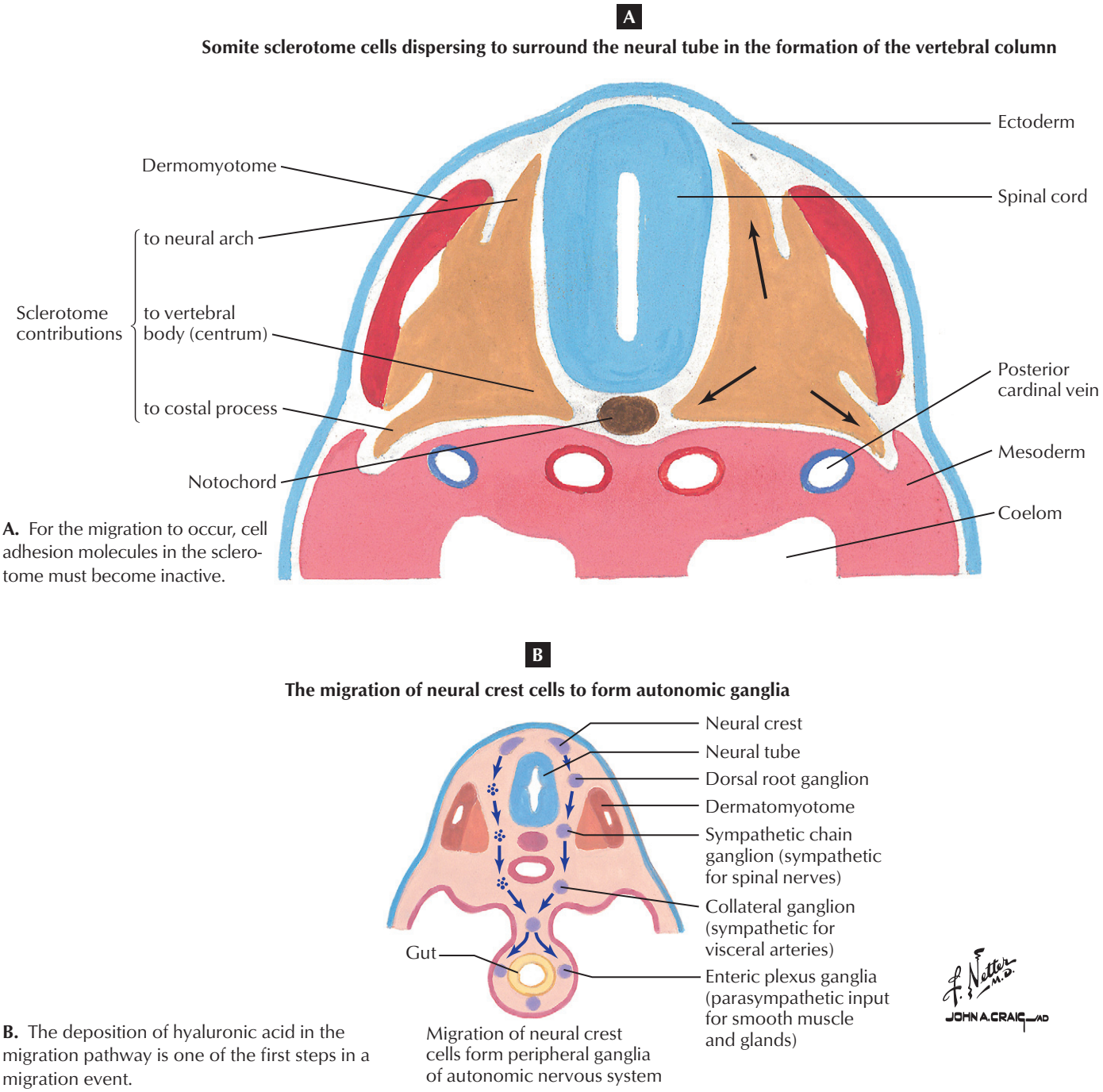


FIGURE 1.11 CELL ADHESION AND CELL MIGRATION

Most events in embryogenesis involve the association, disassociation, and migration of cells. The interrelated processes involve dynamic changes in the molecules expressed in cell membranes. **Cell adhesion molecules** (CAMs) cause cells to aggregate. Their inactivation is a requirement of the initiation of cell migration, but control of the migration pathway is very complex. Trails of connective tissue fibers often help guide cells, a process termed **contact guidance.** Chemical signals may attract cells, and an inhibitory effect of cells bordering the path may also play a role. The deposition of **hyaluronic acid,** a connective tissue protein that binds water, creates a favorable environment for cell migration.

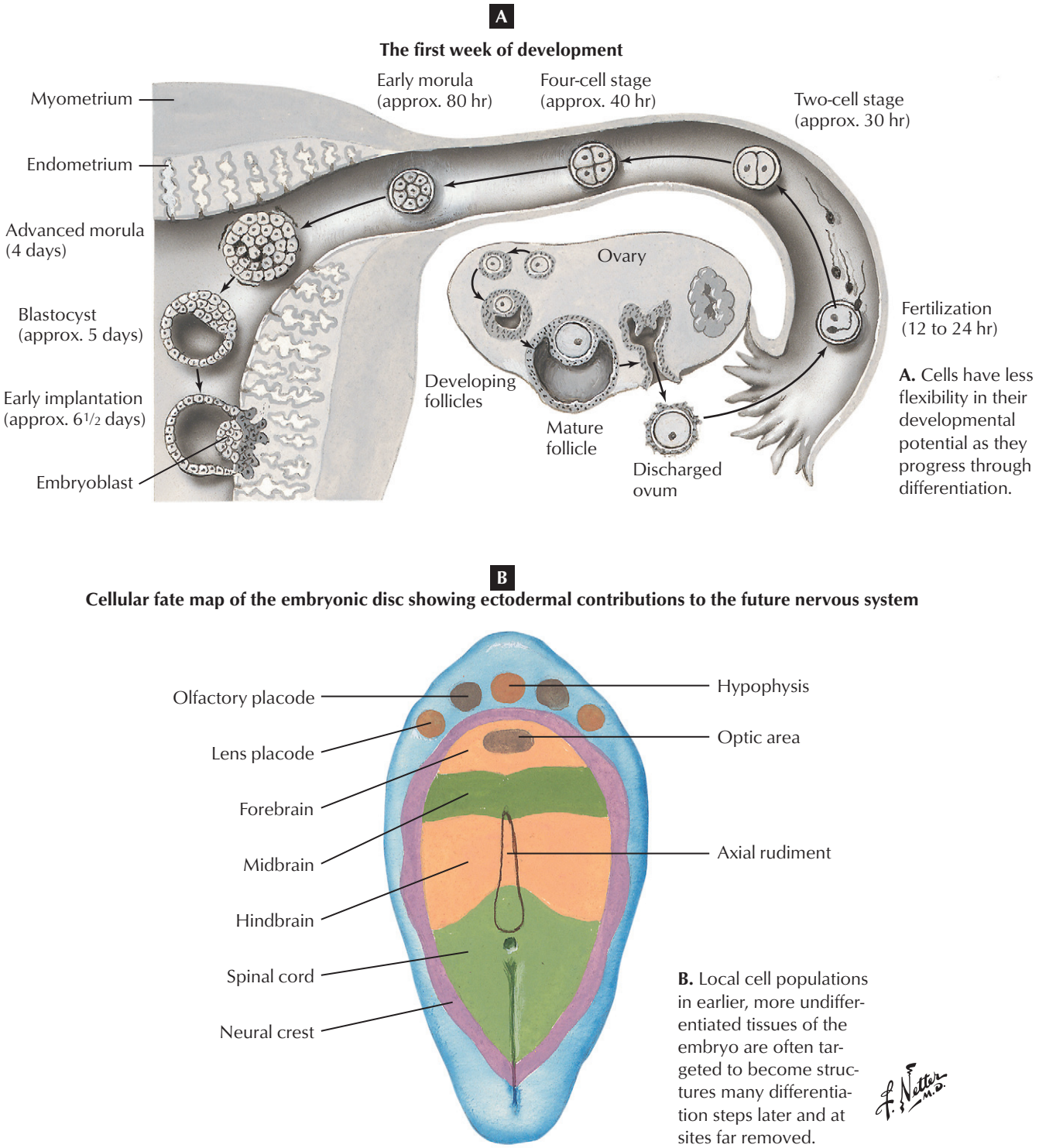


FIGURE 1.12 CELL DIFFERENTIATION AND CELL FATES

Cells in the first few days before the embryo develops are **totipotent.** Each is capable of forming a normal embryo or developing into any of the more than 200 cell types in the body. Cells in the blastocyst, including the early embryo, are **pluripotent,** capable of forming a variety of cell types, but not a whole individual. They are genetically programmed to follow more specific developmental paths. Some undifferentiated **stem cells** remain in adult organs as a source of new cells. These **multipotent** cells can be cultured to form entirely different tissues than in their organ of origin but are thought to have less flexibility in differentiation than embryonic stem cells; they are therefore less attractive for therapeutic and embryonic research.

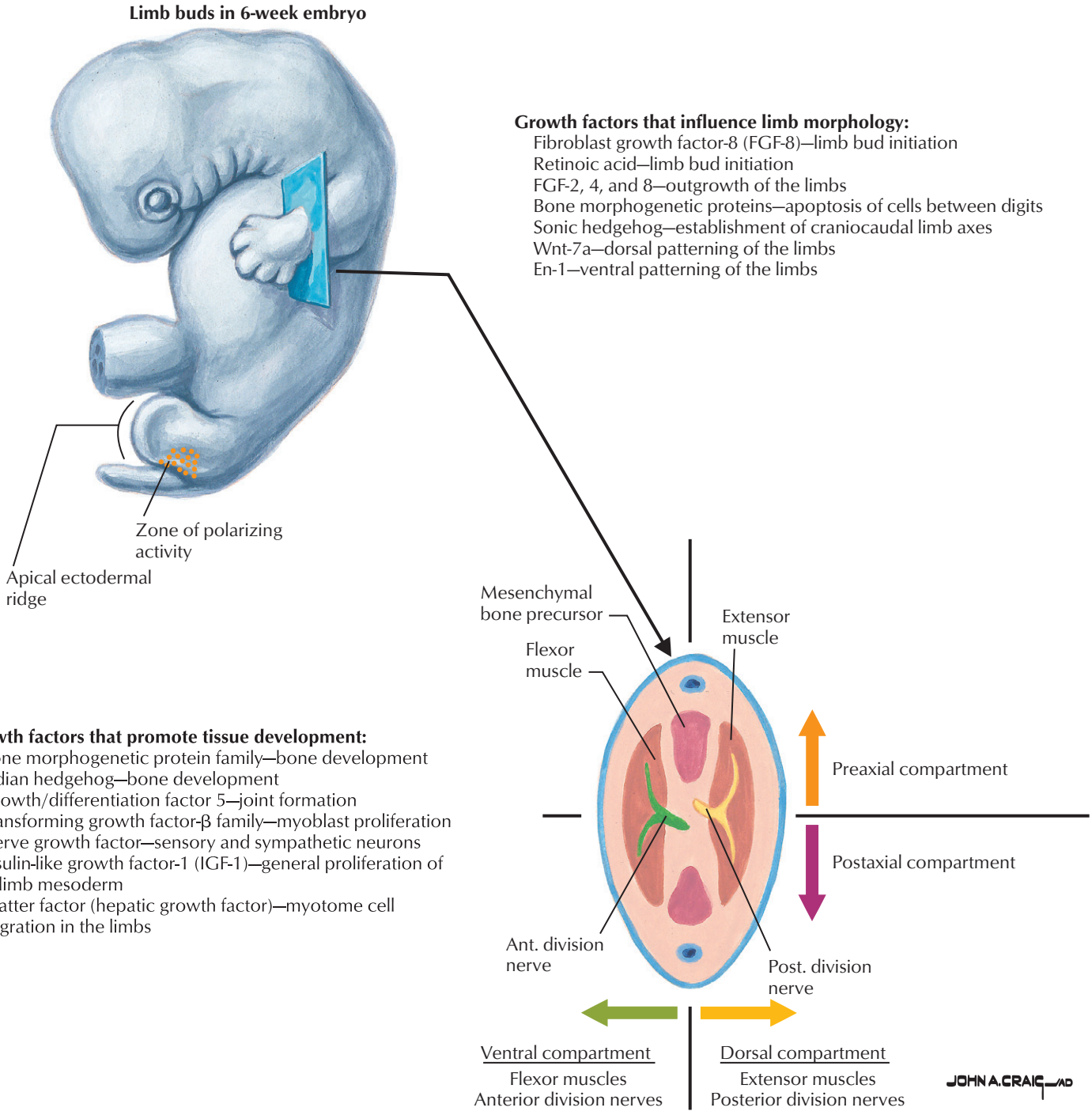


FIGURE 1.13 GROWTH FACTORS

Growth factors are a group of more than 50 proteins that bind to specific cell receptors to stimulate cell division, differentiation, and other functions related to the control of tissue proliferation. They are inducers that can act alone or in combination, but they can affect only cells that express their receptors. Some can stimulate only one cell type (e.g., nerve growth factor), whereas others have broad specificity. Other functions include various roles in cell function, migration, survival, and inhibition of proliferation. Other types of molecules like steroid hormones can have effects similar to growth factors.

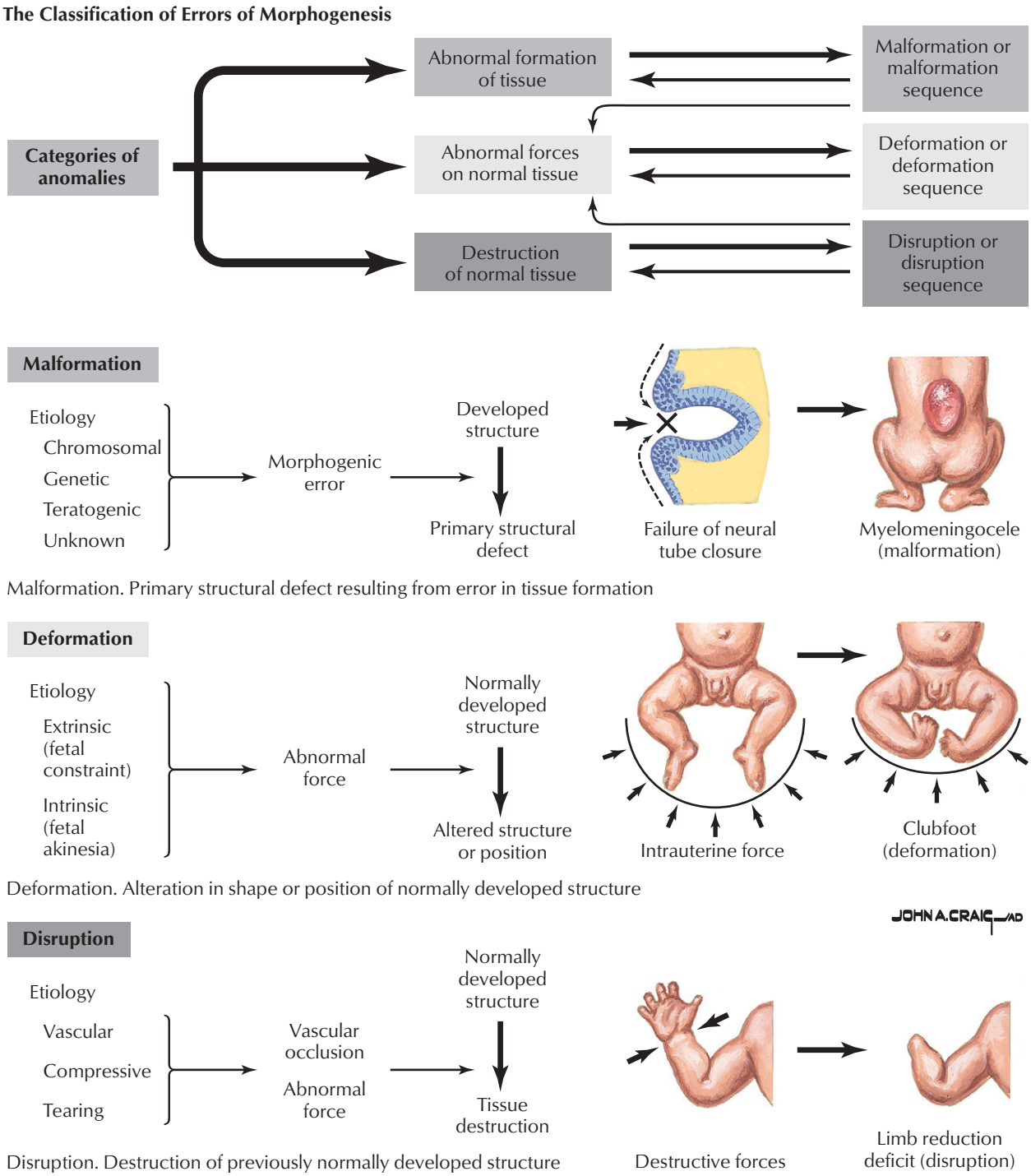


FIGURE 1.14 CLASSIFICATION OF ABNORMAL PROCESSES

There are two broad categories in the classification of developmental defects. Anomalies result from either the abnormal development of a tissue or structure or the secondary deformation or disruption of a normal structure. The first type of malformation can be genetic or produced by external teratogens. The second category includes abnormal forces exerted on a structure from any source, internal or external.

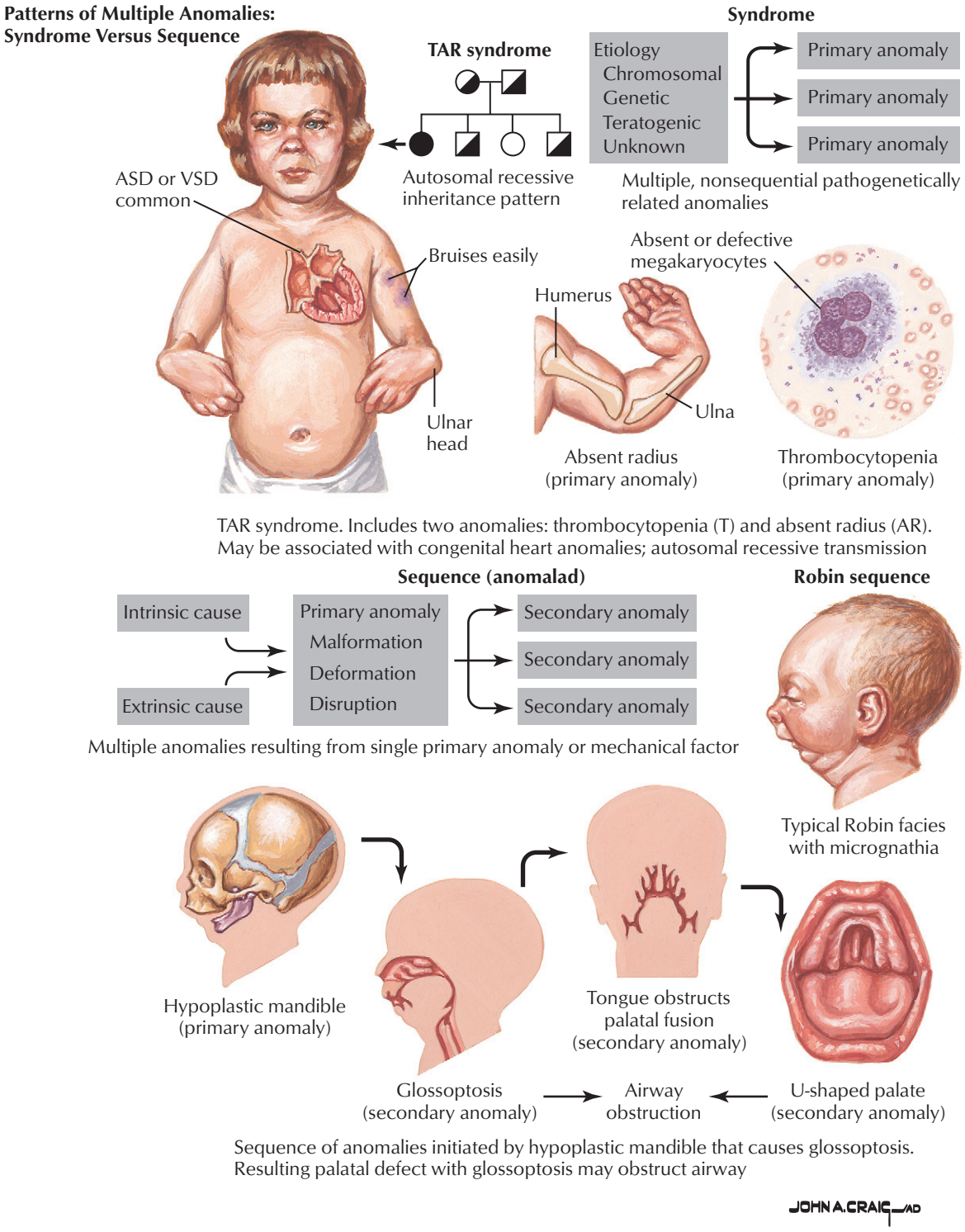
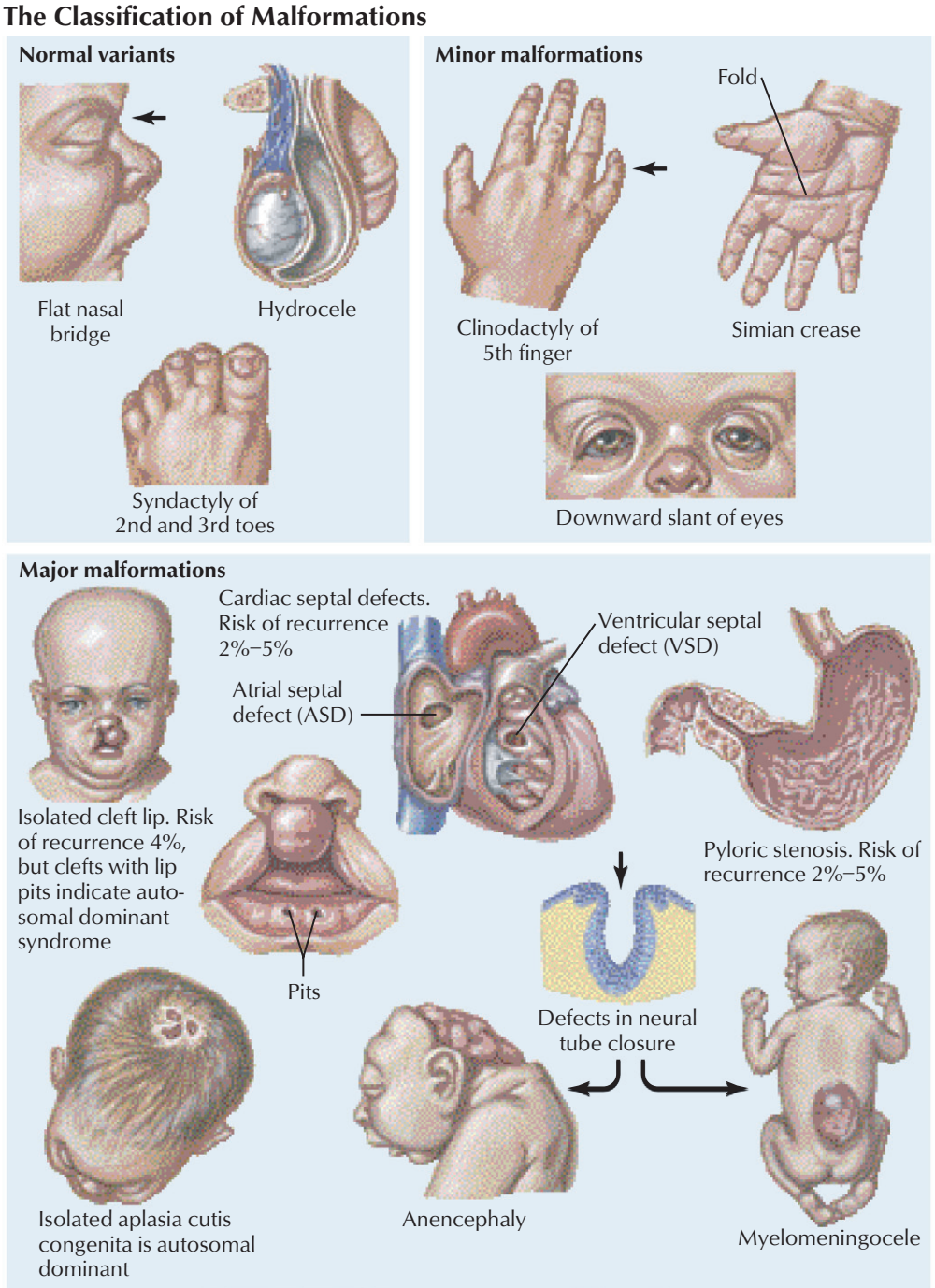


FIGURE 1.15 CLASSIFICATION OF MULTIPLE ANOMALIES

A syndrome is a number of primary, pathogenetically related anomalies from a single cause. A sequence has a primary cause but leads to a cascade of secondary effects. A syndrome is referred to as a disease if the cause is known.



Major and minor malformations may occur as isolated entities or as components of multiple malformation syndrome. Risk of recurrence refers to future pregnancies where normal parents have an affected infant. It depends on the cause of the defect.

FIGURE 1.16 NORMAL VERSUS MAJOR VERSUS MINOR MALFORMATIONS

Defects present in more than 4% of the population are considered normal variations. Minor and major malformations occur in less than 4% of the population and are distinguished from each other by using functional and/or cosmetic criteria. Major and minor malformations may occur as isolated entities or as components of multiple malformation syndromes. The presence of two or more minor anomalies in a newborn may indicate an undetected, major anomaly.

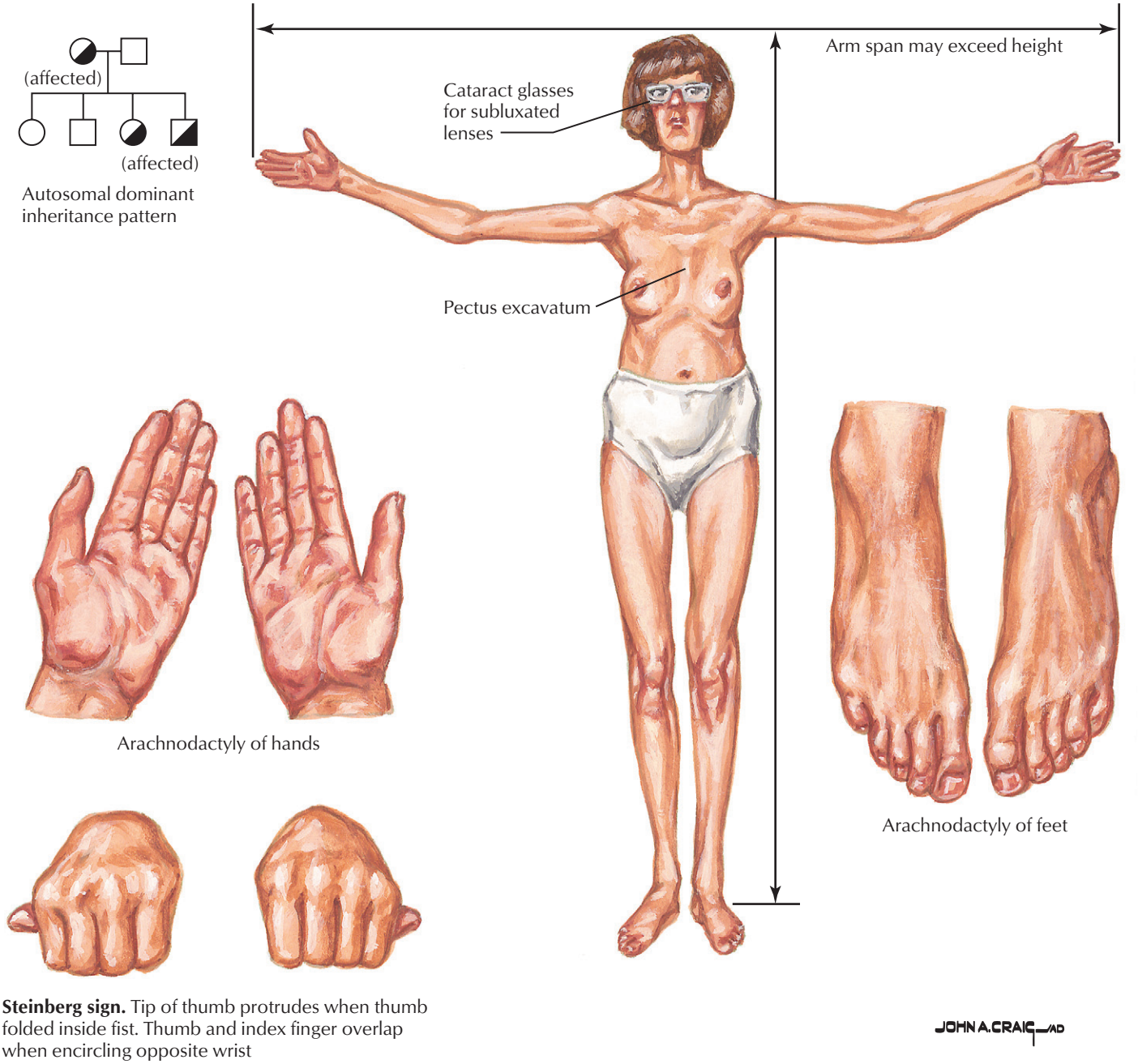


FIGURE 1.17 MARFAN SYNDROME

Marfan syndrome is a **multiple malformation syndrome of postnatal onset** that is inherited in an autosomal dominant pattern. Many cases are linked to advanced paternal age. Although characterized by notable body proportions, subluxated lenses, and a sunken or everted sternum, Marfan syndrome is a progressive connective tissue disorder. The most severe consequences are often in the cardiovascular system, where aneurysms in the aorta or other arteries may result.

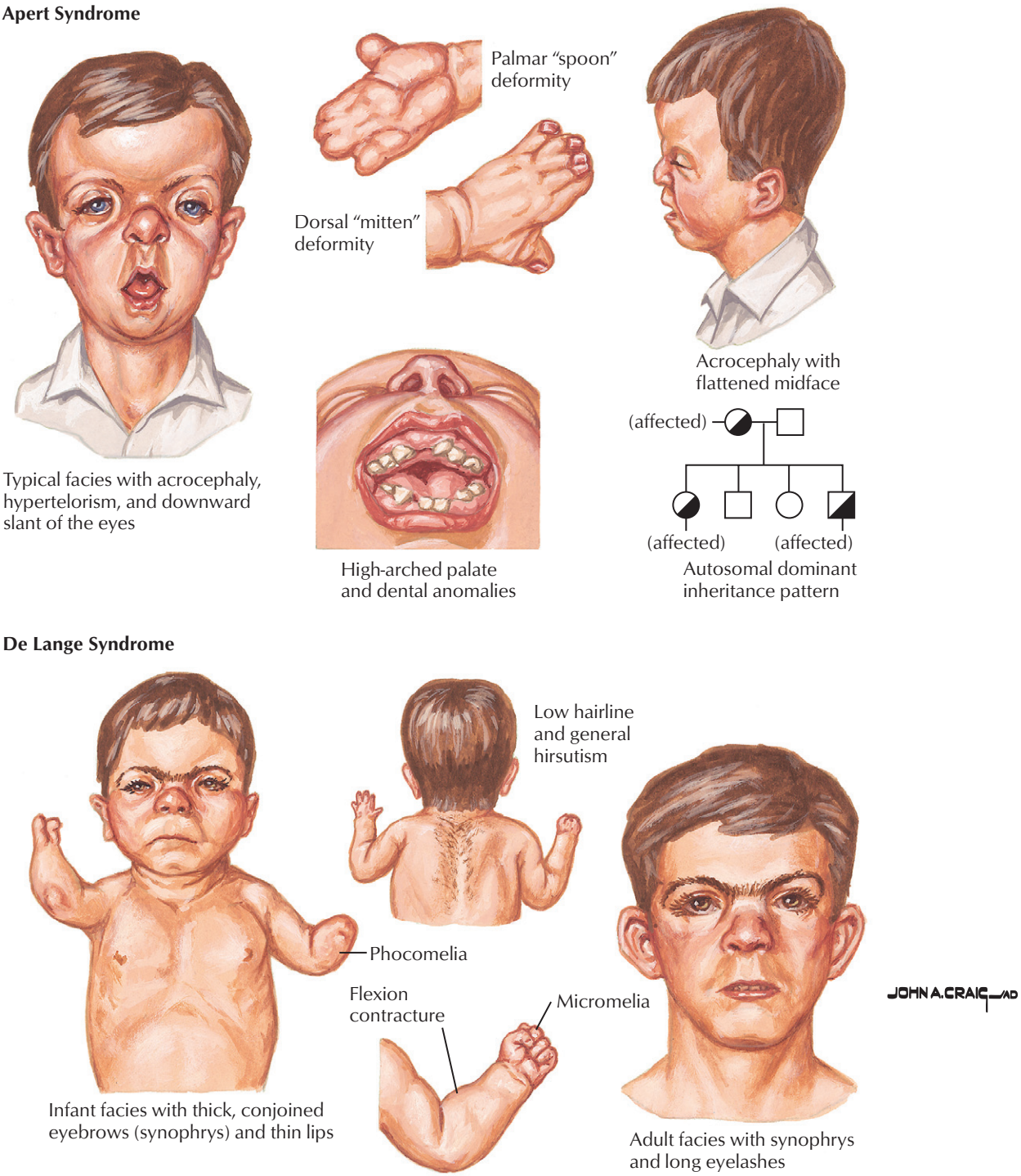


FIGURE 1.18 APERT AND DE LANGE SYNDROMES

Apert and De Lange syndromes are **multiple malformation syndromes of prenatal onset.** Like Marfan syndrome, they are inherited as autosomal dominant mutations, although chromosomal aberrations may be present in De Lange syndrome. In syndromes with prenatal onset and serious defects, affected individuals usually do not reproduce and the syndromes arise as new mutations. Limb malformations, mental retardation, and the facial characteristics shown above typify De Lange syndrome. Premature fusion of the coronal suture is a primary defect in Apert syndrome. The skull is wide and flat with palate and dental defects. Digits in the hand and feet are also fused and may involve the bones. Intelligence is often normal.

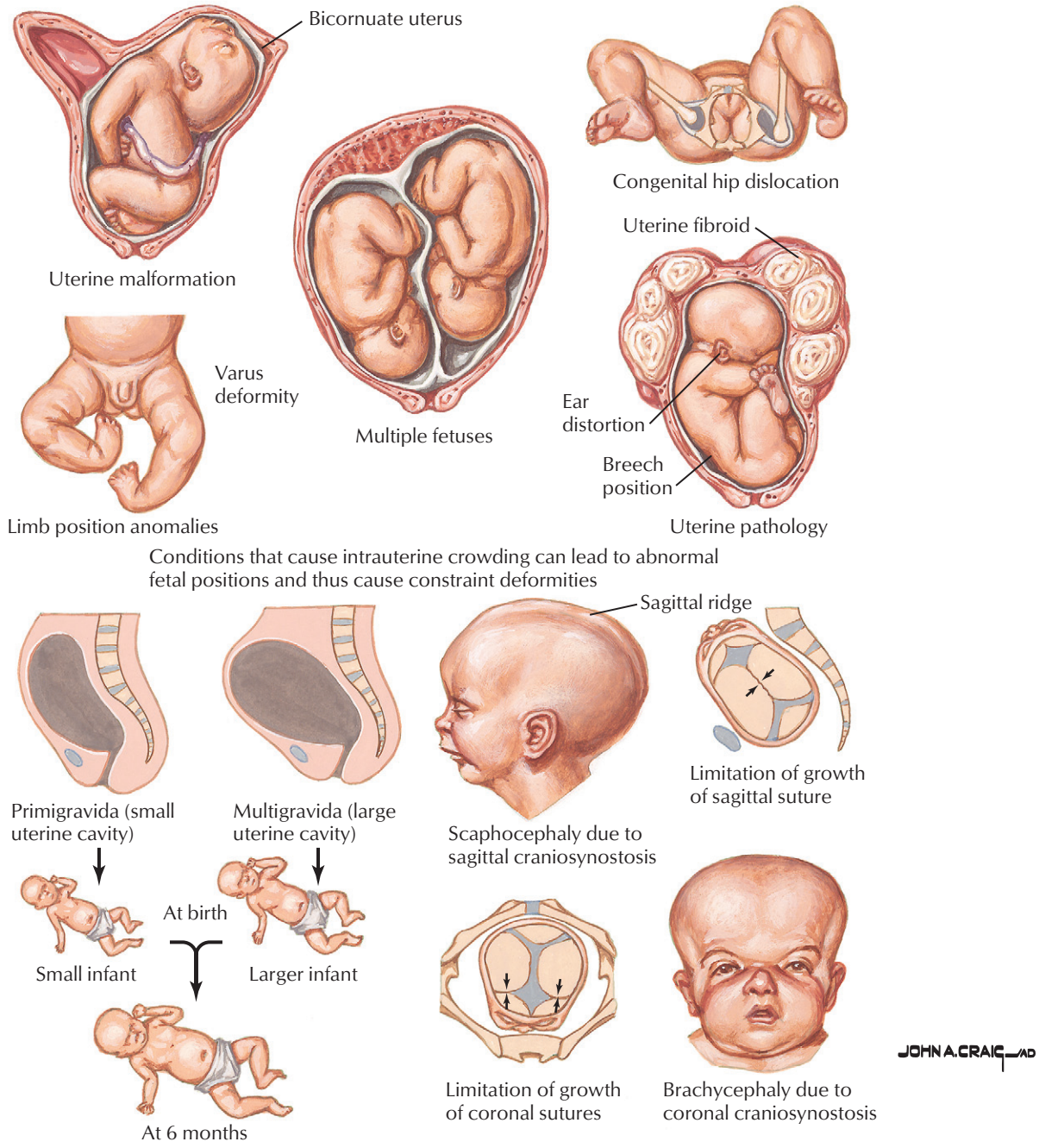


FIGURE 1.19 EXAMPLES OF DEFORMATIONS

Extrinsic deformations are usually related to some type of constraint from uterine pathology or multiple fetuses. Intrinsic deformations are derived from a defect in the fetus (e.g., bone malformations caused by neural or muscle pathology as in clubfoot). Extrinsic constraint may have a single effect or a sequence of defects. The prognosis for deformations is usually excellent. Once the fetus is free of the constraining environment, normal growth and morphology are usually restored.

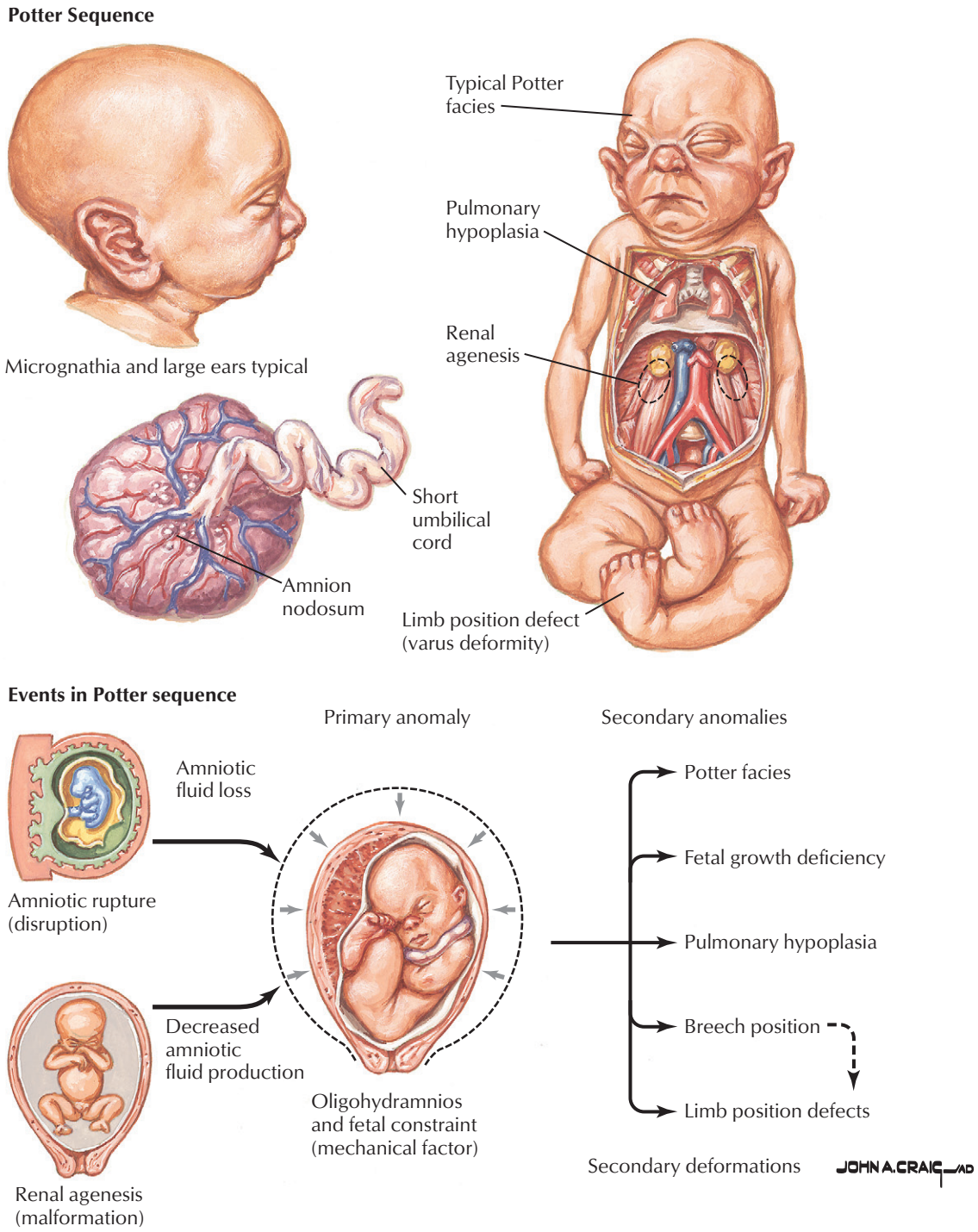


FIGURE 1.20 EXAMPLE OF A DEFORMATION SEQUENCE

This is an example of a primary cause—a decreased amount of amniotic fluid (oligohydramnios)—resulting in a number of secondary effects. The defects in the sequence are caused by a deformation. Malformations and disruptions can also result in a sequence of anomalies. A number of factors can trigger the primary cause, and a malformation (renal agenesis) plus a disruption (rupture of the amnion) initiate this sequence.

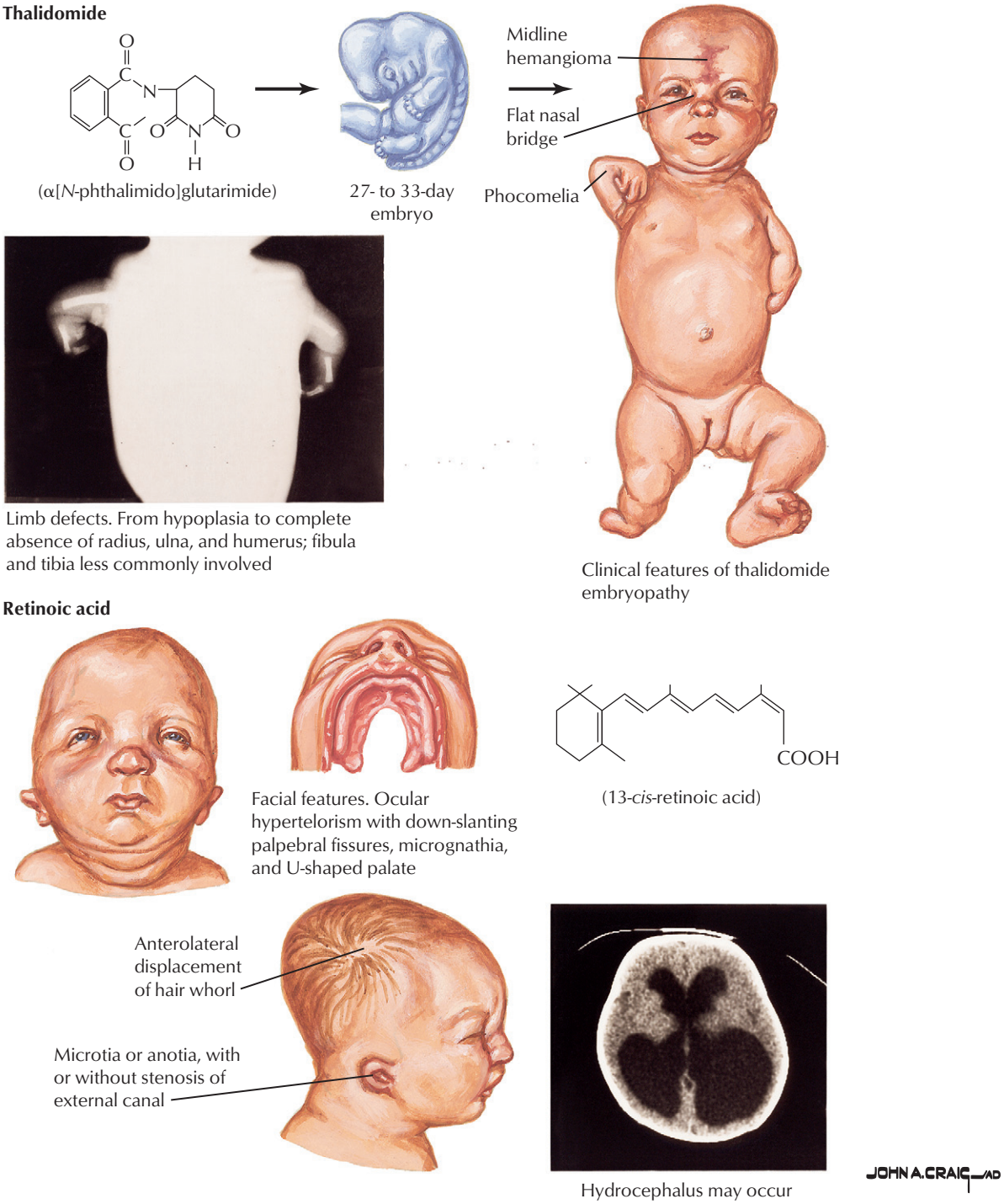


FIGURE 1.21 DRUG-INDUCED EMBRYOPATHIES

Although alcohol is the most common teratogen in humans, thalidomide has one of the most specific mechanisms of action (disruption of blood vessels in the embryonic limb buds). The epidemic of defects it produced between 1959 and 1962 led to research that opened the field of study of drug and chemical agent effects on morphogenesis. Thalidomide, a popular sleeping medication, was discovered to affect the developing embryo in small doses and during a very specific timeframe to produce the characteristic anomalies shown here. Retinoic acid became a common treatment for acne and psoriasis in the 1980s. Both retinoic acid and its cousin, vitamin A, were known teratogens, but many women who were treated with the medication did not know they were pregnant.

Terminology

Anomaly	(G., "irregularity") In embryology and anatomy, an unusual structure that is the result of abnormal development.
Apoptosis	Programmed cell death initiated in mitochondria and usually involving changes in a number of caspase proteins. The result is degradation of DNA and breakup of the cell.
Blastocyst	(G., "germ" + "bladder") Fluid-filled ball of cells that consists of an inner cell mass destined to become the embryo and an outer trophoblast that will be a surrounding membrane (chorion) and the embryonic/fetal contribution to the placenta.
Carnegie stages	A numerical system for characterizing developmental stages. The stages range from 1–23 and cover days 1–56.
Conceptus	All of the products of fertilization, including the embryo, amnion, chorion, yolk sac, allantois, and umbilical cord.
Crown–rump (CR) length	A convenient measure of size of the embryo and fetus, which have varying degrees of curvature. Taken as the maximum, straight-line distance between the top of the head and bottom of the "rump."
Embryo	The developing human through the first 2 months when all of the organ systems are forming.
Etiology	(G., "cause" + "discourse") The study of the causes of diseases or defects. Pathogenesis.
Facies	(L., "Face, surface, or expression") In development, it is the characteristic appearance of a newborn related to congenital anomalies.
Fascia	A layer of connective tissue surrounding muscles, nerves, and vessels or separating tissue layers. It can be dense and sheetlike, or thick, loose connective tissue like the fat-filled superficial fascia under the skin.
Fetus	The developing human from months 3 through 9 (to term).
Fibroblasts	Cells that secrete and maintain the dense and loose connective tissue matrix including all the fibers.
Growth factor	An unsatisfactory historical term derived from the identification of a series of proteins that promote the growth of specific tissues in culture. "Growth" does not characterize the variety of molecular processes and mechanisms in development. Not all "growth factors" are proteins (e.g., retinoic acid), and more recent factors have been identified and named from gene expression studies.
Homeobox	A phylogenetically conservative gene segment of 183 base pairs in many segmentation and homeotic genes (its name is derived from its discovery in the latter). The product, the homeodomain, is a protein segment that binds to DNA as part of the transcription factor function of these regulatory genes.
Homeotic genes	A family of genes, usually transcription factors, that plays a role in determining the fate of body segments in the embryo. They are identified by mutations that cause one segment to become another (e.g., a leg will become an antenna in a fly).
Hyperplasia	(G., hyper- "formation") Abnormal enlargement of an organ or structure due to an increase in the number of cells.
Hypertrophy	(G., hyper- "nutrition") Abnormal enlargement of an organ or structure due to an increase in the size of its cells.

Terminology, cont'd

Hypoplasia	Underdevelopment of an organ or structure.
Keratin	A large family of proteins that forms intracellular filaments and the major component of hair, nails, and outer, protective layer of the skin epidermis (epithelium).
Lamina propria	Histological layer of loose connective tissue beneath the epithelium lining the lumen of a hollow organ.
Lanugo hair	(L., wooly, down) Fine, soft fetal hair that appears around week 12.
LNMP	Last normal menstrual period. Gestational ages are calculated from the estimated time of fertilization or from the last normal menstrual period 14 days before fertilization.
Lumen	(L., "light") Space within a blood vessel or hollow organ.
Malformation	Defect caused by an intrinsic error in a primordium or process.
Malformation sequence	A number of secondary malformations that are a result of a primary malformation. Sequences can also be defects that can be caused by extrinsic factors in deformations and disruptions.
Mesenchyme	Usually considered undifferentiated embryonic connective tissue derived from primitive streak mesoderm or neural crest. Definitions vary depending on whether it is a histological, embryological, or anatomical point of view.
Mesoderm	(G., "middle skin") First interior cells of the embryonic disc that are the product of gastrulation. They are initially in the form of mesenchyme, but some cells quickly condense into longitudinal epithelial columns, a second type of mesoderm.
Monozygotic twins	"Identical" twins resulting from the separation of cells into two distinct populations after fertilization. Heterozygotic twins are from the fertilization of two separate ova.
Morula	(L., "little mulberry") Mass of cells that is the product of early cell division after fertilization.
Multipotent	Capability of adult or some other stem cells to differentiate into a number of cells types but with less flexibility than embryonic totipotent or multipotent stem cells.
Oligohydramnios	(G., "little water in the amnion") Reduction in the amount of amniotic fluid that surrounds and protects the fetus. It is urine produced by the fetal kidneys.
Parenchyma	Epithelial cells of an organ that are metabolically active in the organ's function (e.g., secretory cells in a gland or absorptive enterocytes in the intestine).
Pluripotent	Capability of cells of the blastocyst and early embryo to differentiate into many cell lines, but not a whole individual.
Primordium	(L., "origin") First cellular indication of an organ or structure.
Quickening	Fetal movements felt by the mother.

Terminology, cont'd

Reticular fibers	Small-caliber collagen fibers with sugar groups that are predominant in the stroma of lymphatic organs. They are also present in general connective tissue matrix along with larger collagen fibers and elastic fibers.
Somites	Epithelial blocks of mesoderm that flank the neural tube and give rise to bone (from the sclerotome of a somite), muscle (from the myotome), and connective tissue (from the dermatome). They can serve as convenient indicators of developmental stages from 20–30 days (e.g., "4-somite stage").
Stem cell	Undifferentiated cell in the embryo or adult that is capable of forming many cell types. The earlier in development, the more flexibility for differentiation.
Stroma	The supporting, connective tissue framework of an organ.
Syndrome	(Gr., "running together") Combination of primary symptoms/abnormalities that results from a particular genetic or environmental cause and is not a sequence of secondary defects.
Teratology	Study of abnormal development. A "teratogen" is an agent that causes birth defects.
Totipotent	Capability of the cells formed soon after fertilization to each develop into a whole human being or any of its cells.
Transcription	Making messenger RNA from DNA in chromosomes in the cell nucleus, the first step in the creation of proteins. The initiation and regulation of transcription is a fundamental process controlling cell and tissue differentiation.
Translation	The "translation" of the sequence of nucleotide bases in messenger RNA into protein amino acid sequences via transfer RNA in ribosomes.
Trimester	Clinical division of the prenatal period into three 3-month segments. The organ systems develop in the first and the fetus is potentially viable after the second.
Trophic	(Gr., "nourishing") An influence on an organ or structure that promotes its general growth and sustenance.
Tropic	(Gr., "a turn, turning") Developmental response of a cell or structure to an external stimulus, such as growing toward a chemical secretion.
Vernix caseosa	(L., "varnish") A greasy, protective covering of the fetal skin that develops at week 18. It consists of dead epidermal cells, the secretion of sebaceous glands, and lanugo hair.
Zygote	(Gr., "union") Cell product of fertilization, the union of the sperm and egg. It is the beginning of development.

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CHAPTER 2

EARLY EMBRYONIC DEVELOPMENT AND THE PLACENTA

Early Embryonic Primordia

Inner cell mass, ectoderm, endoderm, primitive streak and node (knot) of ectoderm, and mesoderm derived from the latter two ectodermal structures.

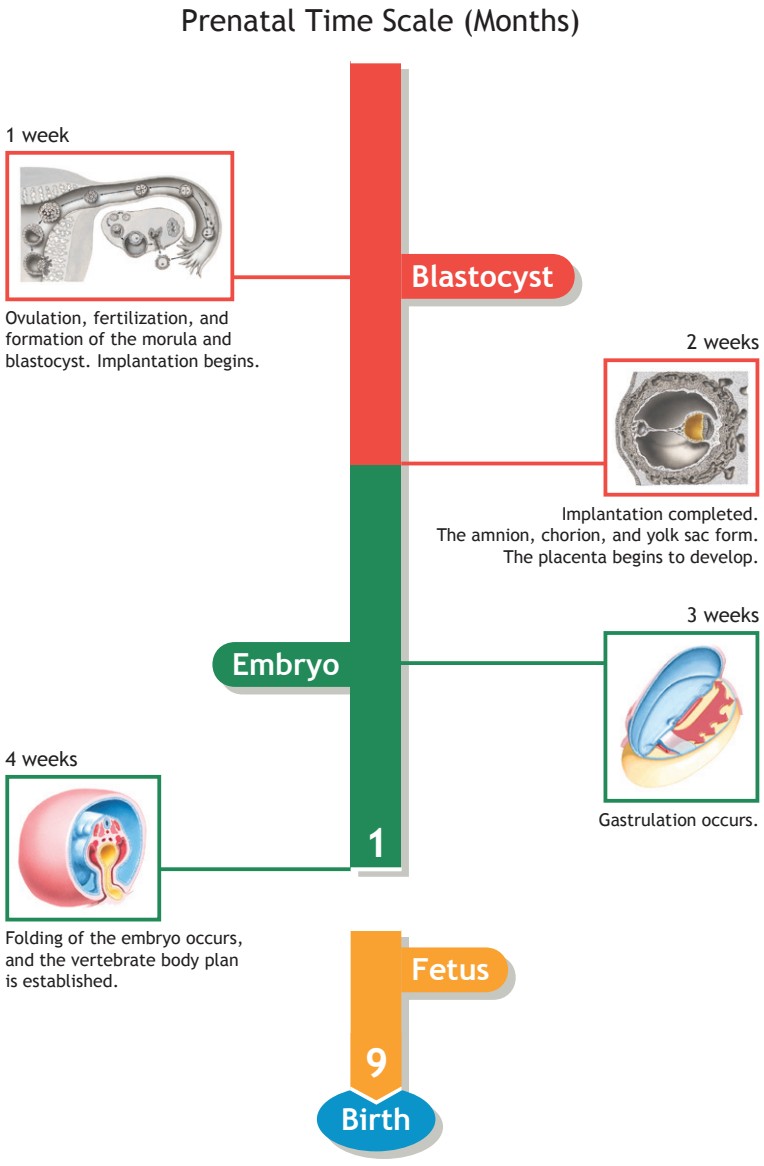
Primordia of the Gastrula and Cylindrical Embryo

Notochord, somites (from paraxial columns), intermediate mesoderm, lateral plate enclosing the intraembryonic coelom, somatopleure, splanchnopleure, gut tube and mesenteries, cardiogenic mesoderm, neural crest, and neural tube.

Plan

The embryonic gastrula, a trilaminar disc of ectoderm, endoderm, and mesoderm, is continuous with the amnion above it and yolk sac below. Coeloms form in the lateral plate mesoderm, dividing it into a somatic component with the ectoderm (somatopleure) and a splanchnic component with the endoderm (splanchnopleure). As the trilaminar embryonic disc folds into a cylinder, the endoderm folds into a gut tube extending the length of the embryo with a surrounding coelom that separates it from the somatopleure body wall. Segmentation is established in the paraxial columns and developing nervous system. By the end of the first month, all of the basic organ and tissue relationships seen in the adult are established.

Timeline



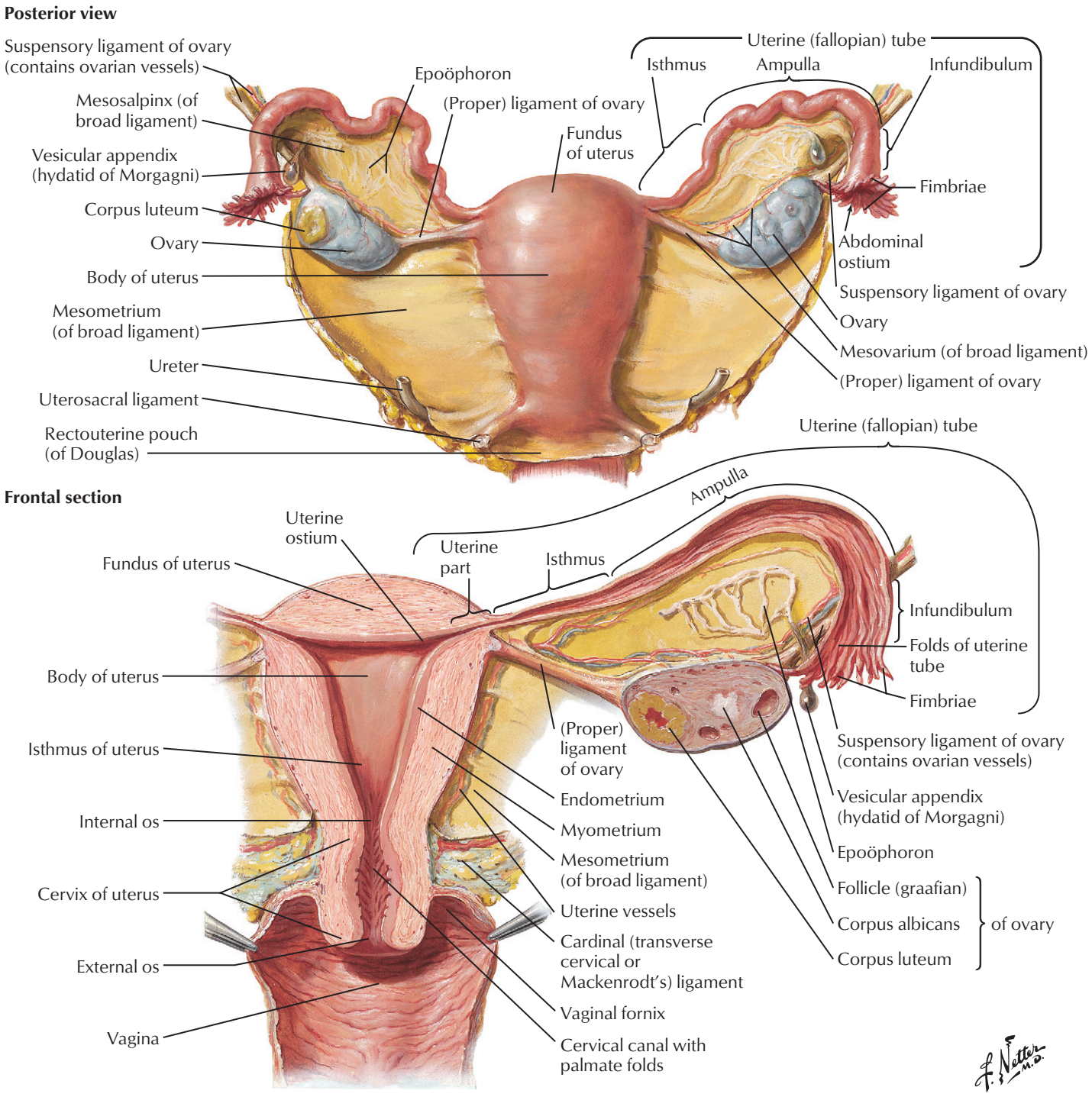


FIGURE 2.1 ADULT UTERUS, OVARIES, AND UTERINE TUBES

The uterus, uterine tubes, and ovaries are enclosed by the **broad ligament (mesometrium),** a transverse fold of visceral peritoneum across the pelvic floor. The upper part of this mesentery is the **mesosalpinx,** the mesentery of the uterine tubes. A posterior extension of the broad ligament investing each ovary and fibrous ovarian ligament is the **mesovarium.** The uterine tubes terminate in finger-like **fimbriae** that envelop the ovary at the time of ovulation. Like most hollow organs, the uterus has a thick wall of smooth muscle, the **myometrium,** and an inner mucosal lining of loose connective tissue and epithelium, the **endometrium,** where development takes place.

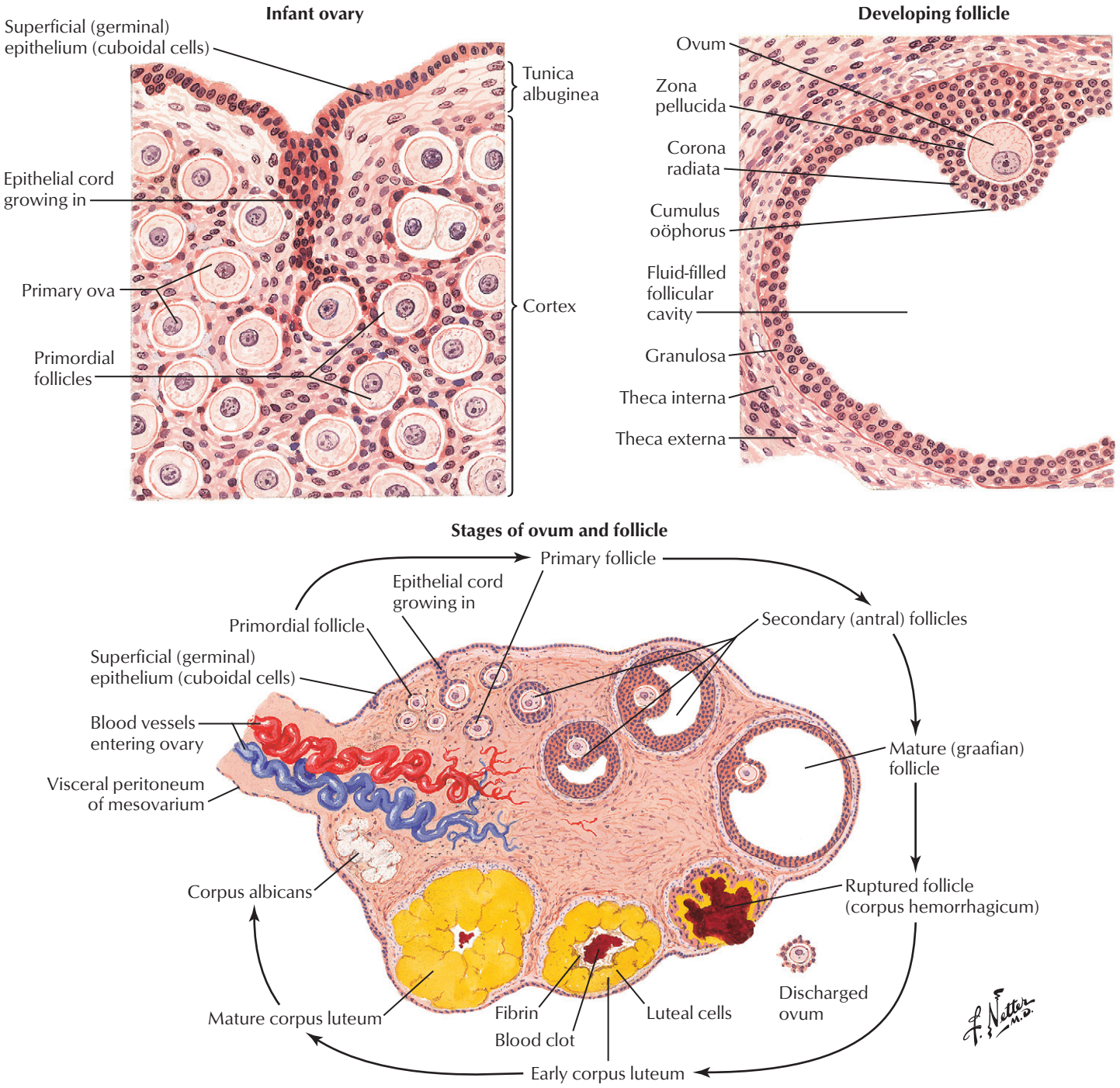


FIGURE 2.2 OVARY, OVA, AND FOLLICLE DEVELOPMENT

The ovary is an exocrine and endocrine organ composed of loose connective tissue, a fibrous capsule, and a **germinal epithelium** continuous with the peritoneum of the mesovarium. Its exocrine process is ovulation. Each ovary has approximately 400,000 oocytes at birth, and each month in the reproductive years, a few begin to develop in hormone-secreting **follicles.** Typically, only one follicle reaches maturity and ruptures to release the oocyte from the ovary. After ovulation the follicle becomes the **corpus luteum.** Follicular hormones control the timing of ovulation, and the corpus luteum prepares the uterus for pregnancy. If pregnancy occurs, the corpus luteum greatly enlarges to maintain the pregnancy and develop the mammary glands (in conjunction with placental hormones).

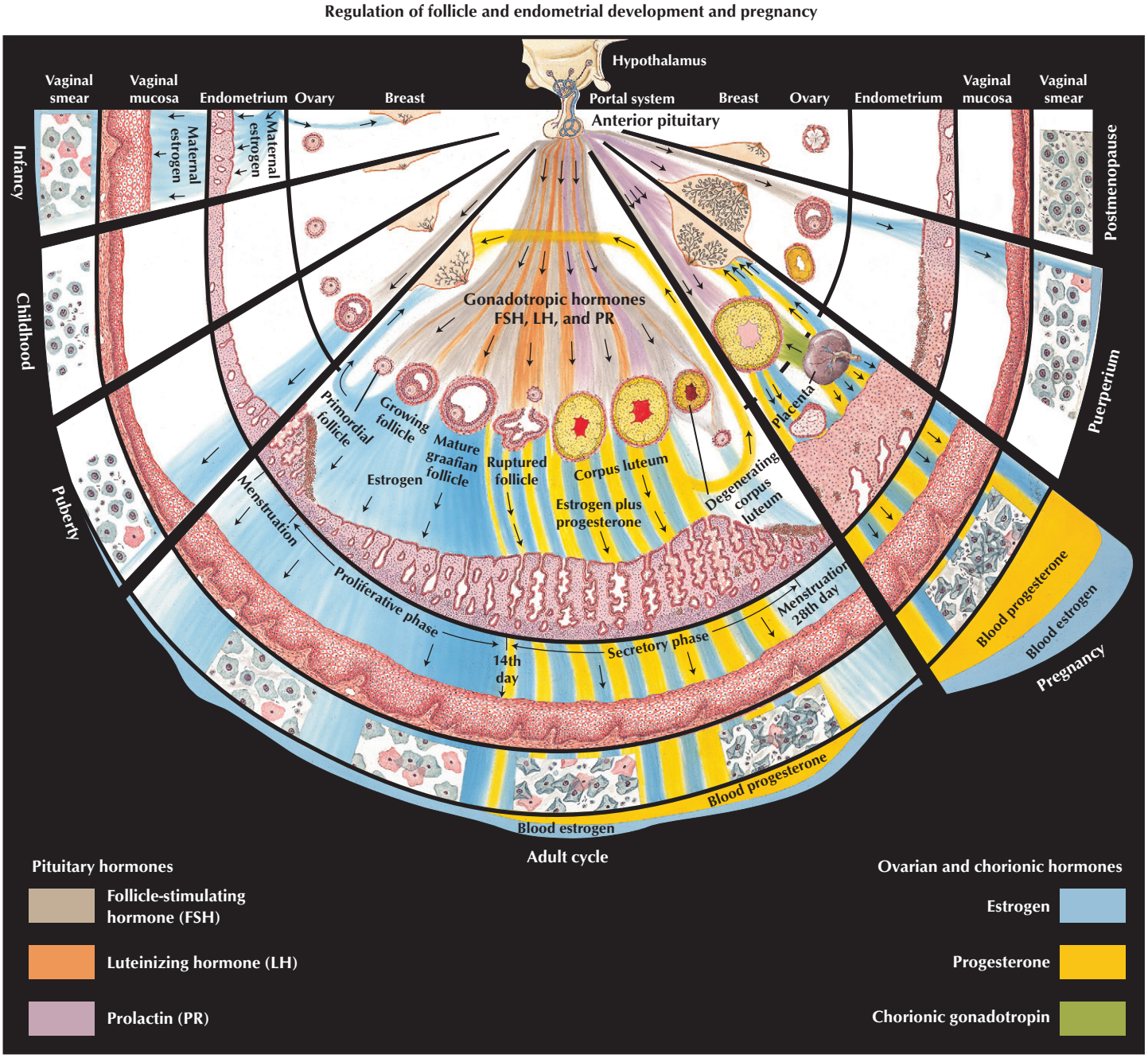


FIGURE 2.3 THE MENSTRUAL CYCLE AND PREGNANCY

Gonadotropic hormones from the hypothalamus cause the anterior lobe of the pituitary gland (pars distalis) to release **follicle-stimulating hormone** (FSH) and **luteinizing hormone** (LH). These hormones stimulate the development of ovarian follicles, which in turn secrete **estrogen.** Rising estrogen levels trigger a surge of LH. This results in ovulation and the development of the corpus luteum, which begins to secrete **progesterone** and estrogen. Progesterone builds up the endometrial wall in preparation for implantation (pregnancy). Progesterone also inhibits LH, so if no pregnancy occurs, the corpus luteum causes its own demise. If a pregnancy occurs, the placenta produces **human chorionic gonadotropin** (hCG) to maintain the corpus luteum and pregnancy.

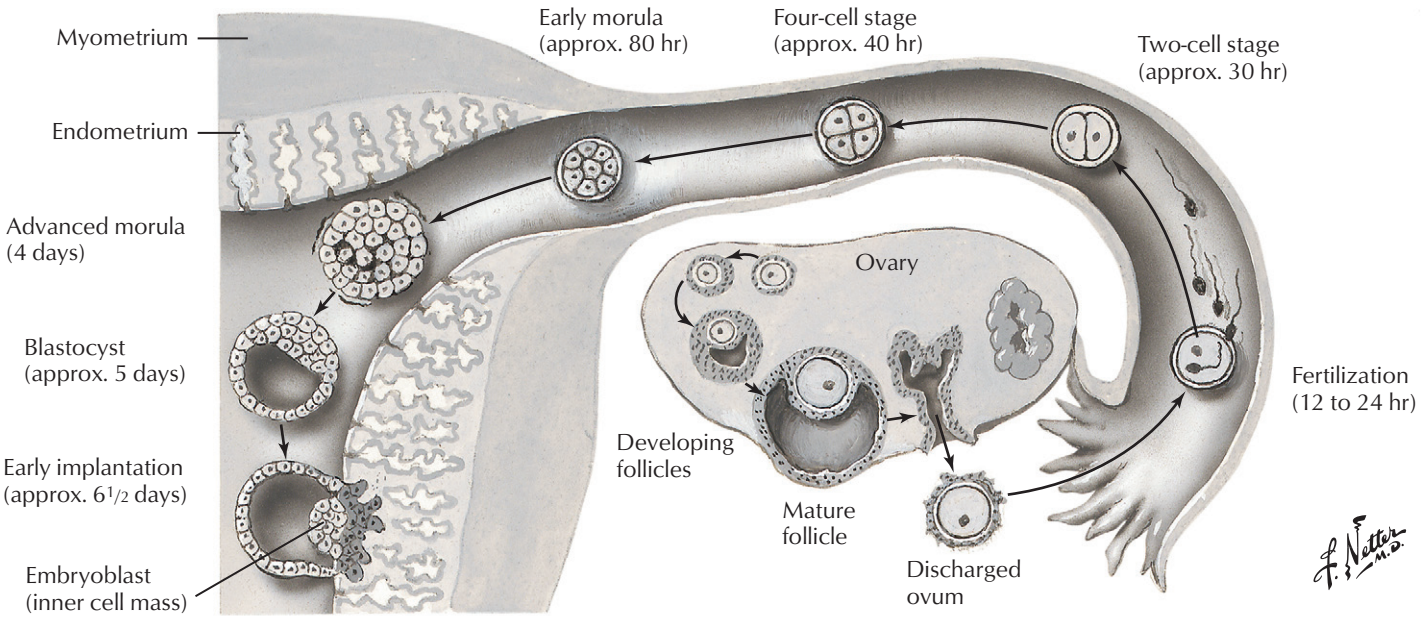


FIGURE 2.4 OVULATION, FERTILIZATION, AND MIGRATION DOWN THE UTERINE TUBE

Ovulation occurs when a maturing egg (**ovum**) is released from an **ovarian follicle** at the surface of the ovary. **Fimbriae** of the uterine tube cover the ovary and guide the ovum into the uterine tube. **Conception,** or **fertilization,** occurs in the distal third of the uterine tube. A **zygote** forms when the sperm and egg nuclei unite. Cell division results in two-, four-, and eight-cell stages in the uterine tube. By 3 to 4 days, a tight ball of cells termed the **morula** is ready to enter the uterine cavity. Near the end of the first week, the morula becomes the fluid-filled **blastocyst** with an **inner cell mass** (embryoblast) and outer **trophoblast.** The blastocyst adheres to the uterine mucosa (usually high up on the posterior wall) and sinks within it during **implantation.**

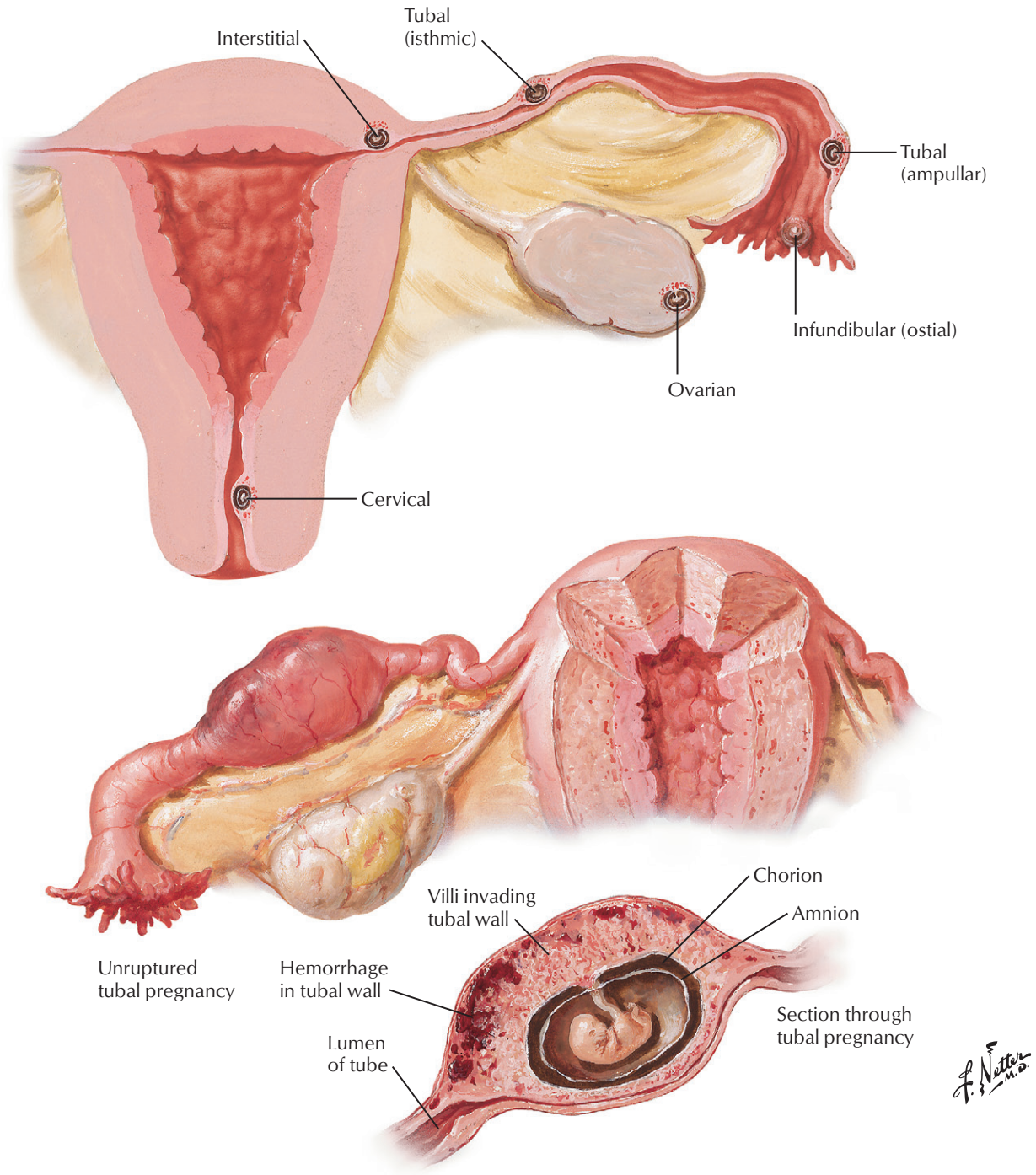


FIGURE 2.5 ECTOPIC PREGNANCY

An ectopic pregnancy results from the implantation of the blastocyst in an abnormal location. It can occur on the surface of the ovary or anywhere along the path of migration into the uterine cavity. Implantation can occur at any location within the uterus, including the cervix, although the latter is extremely rare. The most common ectopic implantation site (95%) is within the uterine tube.

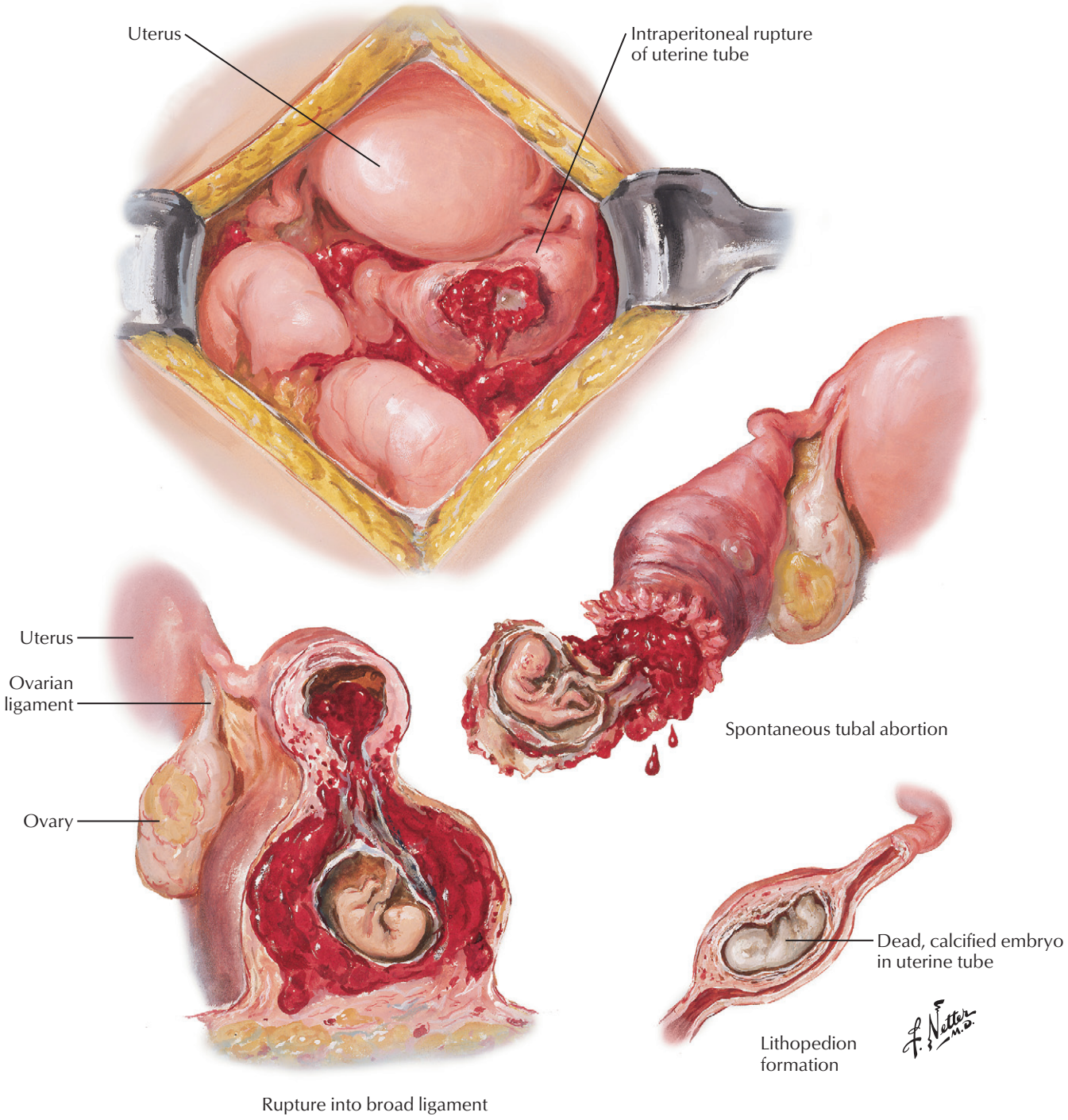


FIGURE 2.6 TUBAL PREGNANCY

Tubal pregnancies are common ectopic sites that can lead to maternal mortality if undetected. Unlike the uterus, the uterine tubes are not capable of expanding, and the likelihood of tubal rupture and hemorrhage increases from the second through the fifth months.

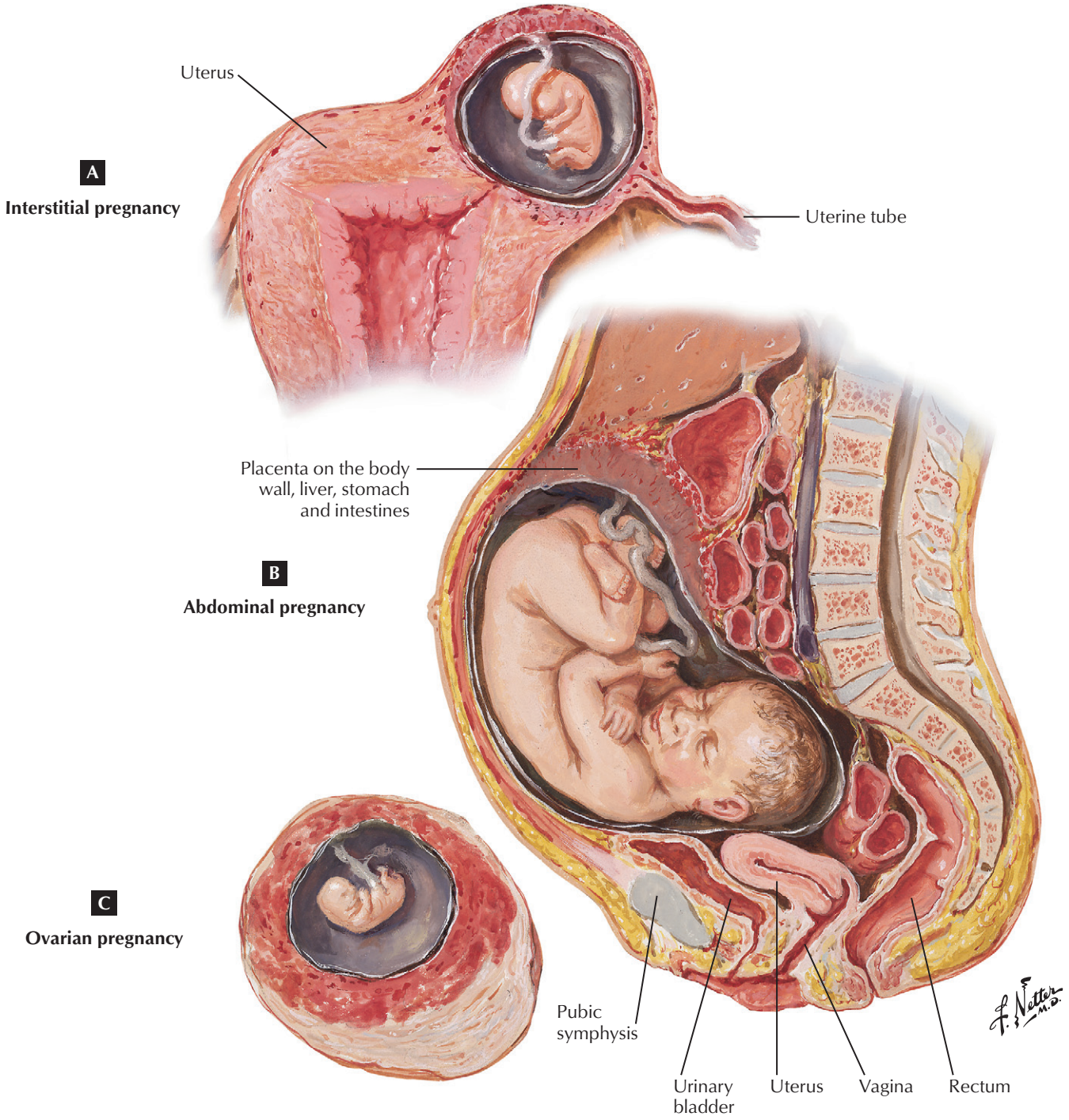


FIGURE 2.7 INTERSTITIAL, ABDOMINAL, AND OVARIAN PREGNANCY

Shown in part A is an ectopic pregnancy in the interstitial, uterine part of the uterine tube. Because the uterine tubes are not physically connected to the ovary, it is possible for a fertilized oocyte or spontaneously aborted conceptus in the distal uterine tube to escape into the pelvic or abdominal cavity with implantation on the ovary (C), uterus, urinary bladder, or any abdominal organ or mesentery (B). A placenta can form on most tissues or structures, and development can proceed to term outside of the uterus. This is extremely rare, and abdominal pregnancies usually have considerable bleeding because of gastrointestinal organ movement and the unstable environment for the placenta.

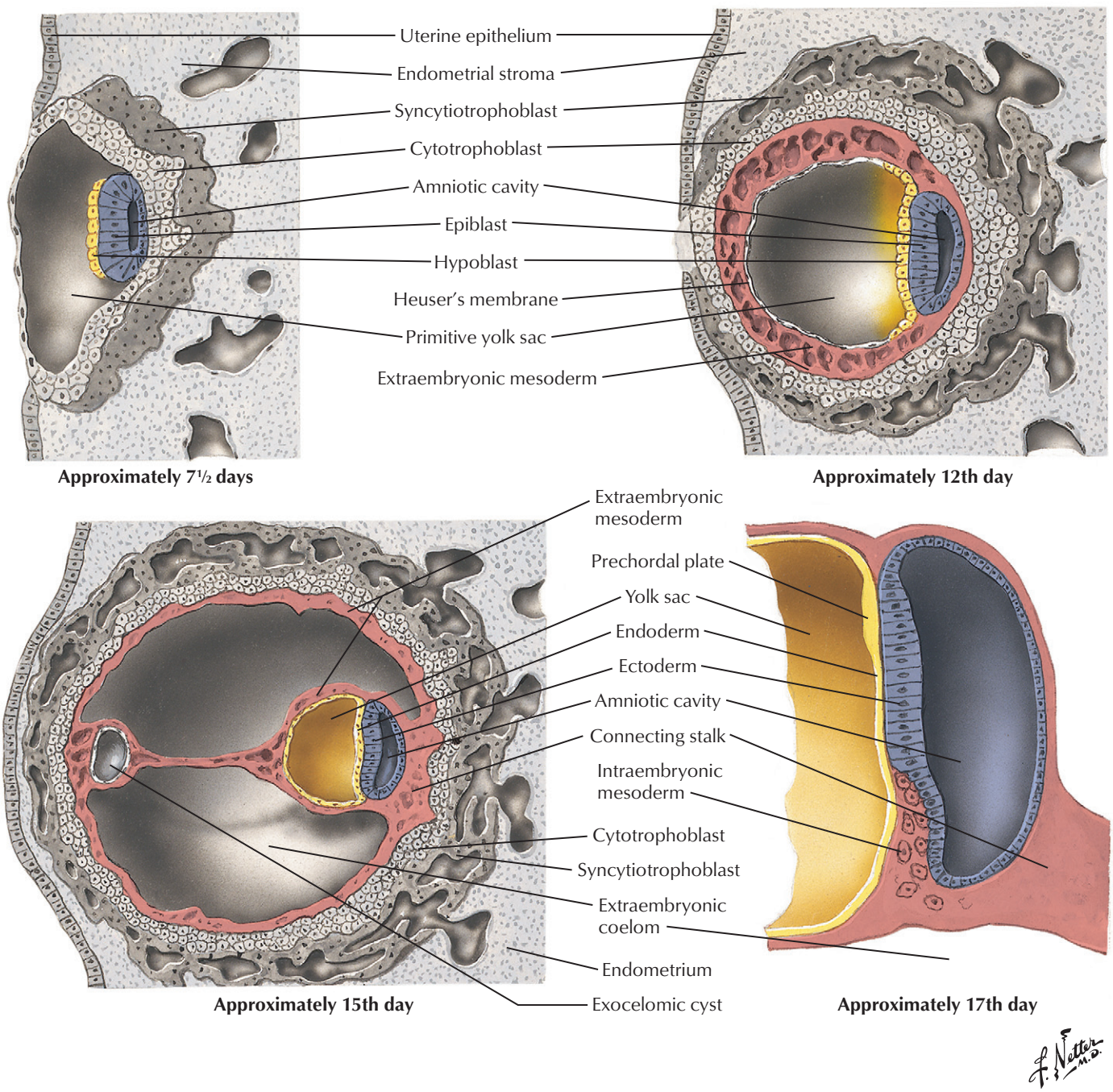


FIGURE 2.8 IMPLANTATION AND EXTRAEMBRYONIC MEMBRANE FORMATION

The trophoblast develops two layers: an outer **syncytiotrophoblast** (or syntrophoblast) and inner **cytotrophoblast.** The inner cell mass develops into two cell types: a columnar epithelial **epiblast** and cuboidal **hypoblast.** The epiblast cell mass becomes hollow to form the fluid-filled primitive amniotic cavity. The hypoblast cells form a simple squamous primitive yolk sac (Heuser's membrane). A second wave of hypoblast cell migration displaces the primitive yolk sac. Extraembryonic mesoderm coats the old blastocyst cavity to complete the extraembryonic membranes. The trophoblast is now the three-layered **chorion.** Mesoderm and endoderm (former hypoblast cells) form the definitive yolk sac. Mesoderm and ectoderm (former epiblast cells) form the definitive amnion.

Formation of Intraembryonic Mesoderm from the Primitive Streak and Node (Knot)

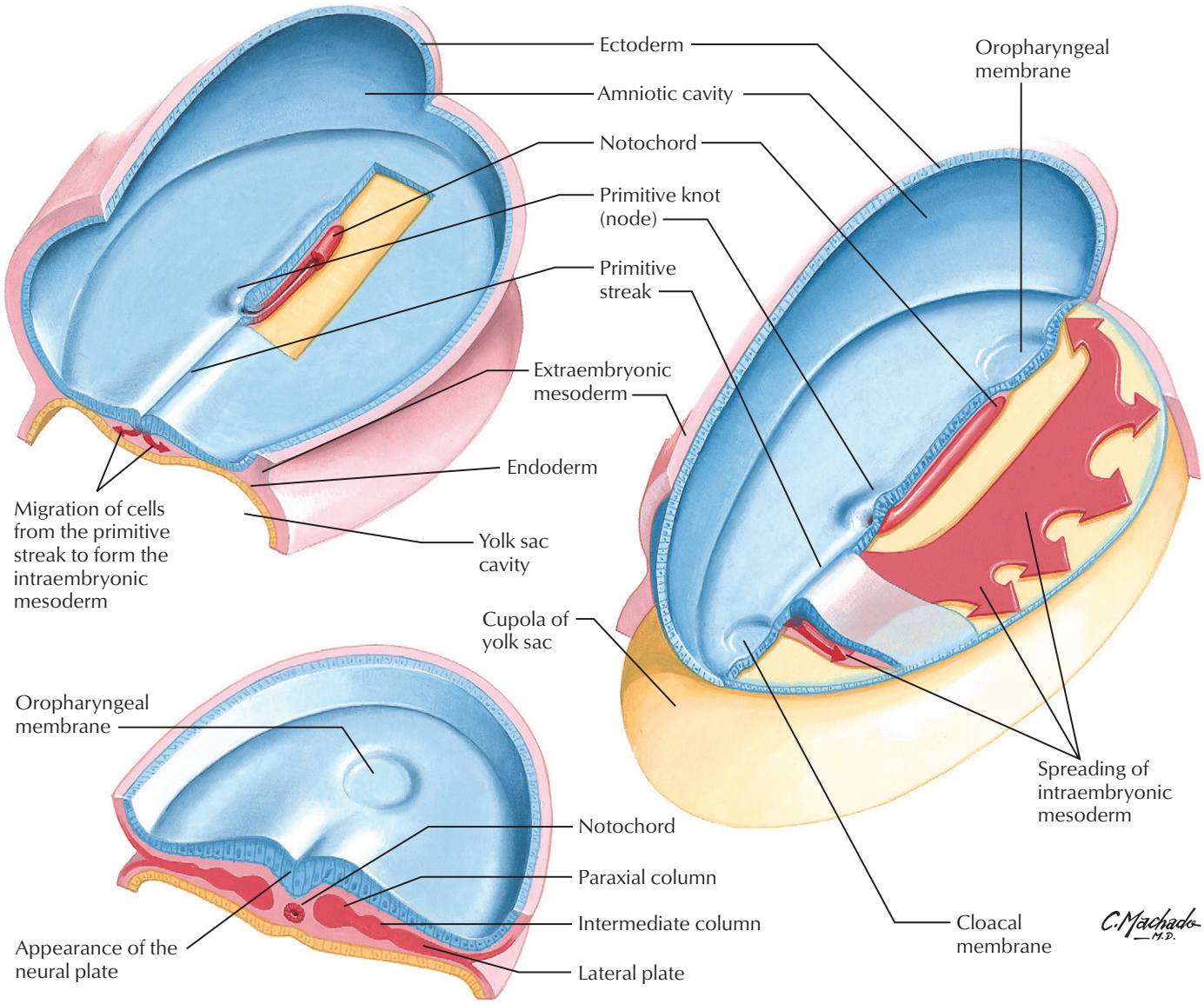


FIGURE 2.9 GASTRULATION

Gastrulation is the production of intraembryonic mesoderm from thickenings of ectoderm—the primitive streak and primitive knot (or node). The latter forms a midline cord of mesoderm, the notochord. The primitive streak gives rise to the rest of the intraembryonic mesoderm, including the cardiogenic mesoderm in front of the oropharyngeal membrane. Gastrulation is complete when the intraembryonic mesoderm condenses into columns flanking the notochord: paraxial columns (future somites), intermediate mesoderm, and lateral plates. The mesoderm between the columns is in the form of mesenchyme, the loose embryonic connective tissue that surrounds structures in the embryo. The primitive streak and node recede toward the tail end of the embryo and disappear.

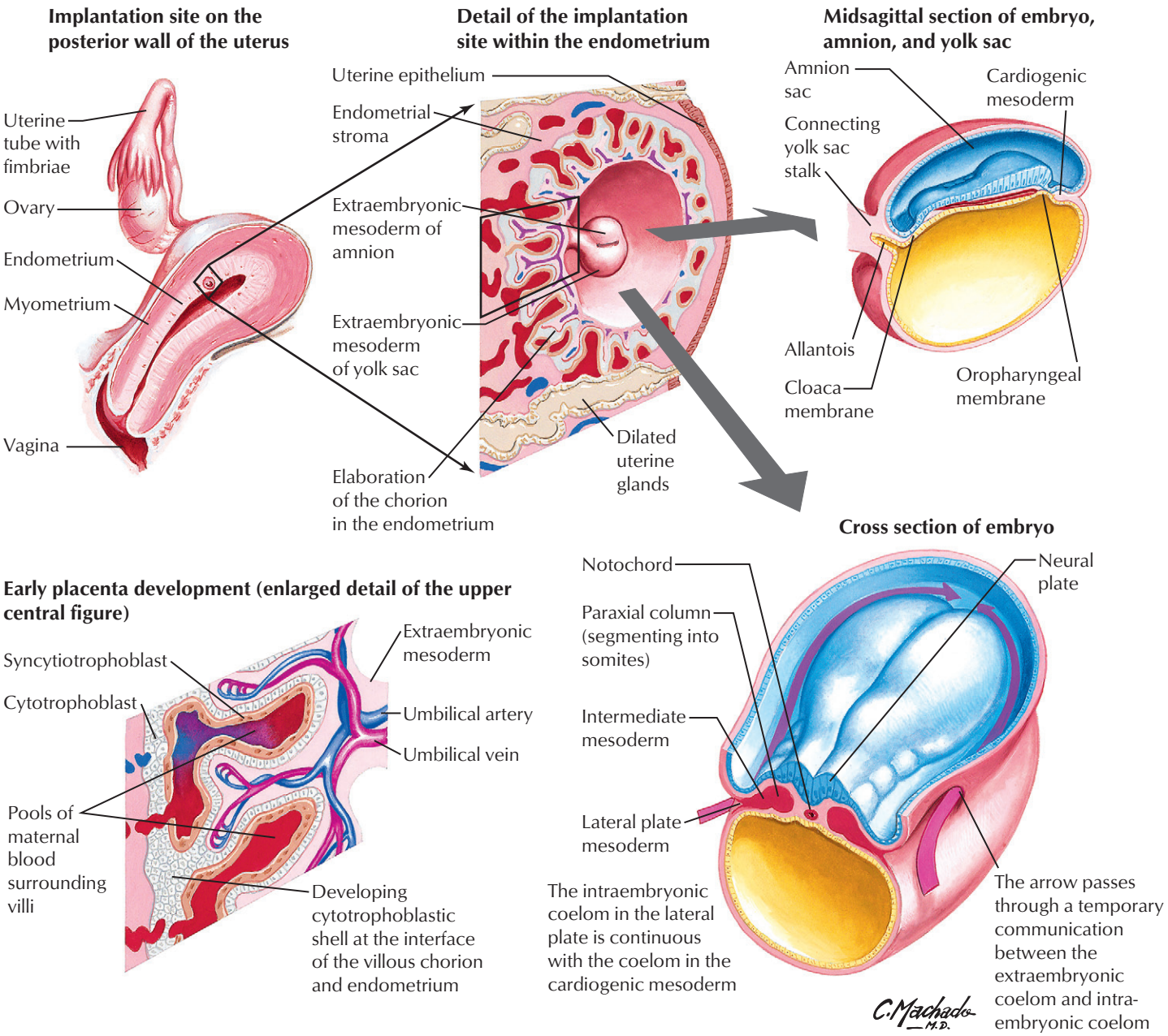


FIGURE 2.10 NEURULATION AND EARLY PLACENTA AND COELOM DEVELOPMENT

Concurrent with gastrulation are the first steps in the formation of the nervous system, heart, placenta, umbilical cord, and intraembryonic coelom (body cavities). Primordia include neural plate ectoderm in front of the primitive streak, cardiogenic mesoderm in front of the oral membrane, and a hollowing of the lateral plate to form an intraembryonic coelom. The placenta develops from the chorion. The connecting stalk between embryo and placenta shifts toward the tail end of the embryo to form the umbilical cord. Oral and cloacal membranes are sites of the future mouth and anus, respectively. The allantois is a vestigial extraembryonic membrane in humans consisting of an endodermal evagination of the yolk sac into the mesoderm of the connecting stalk.

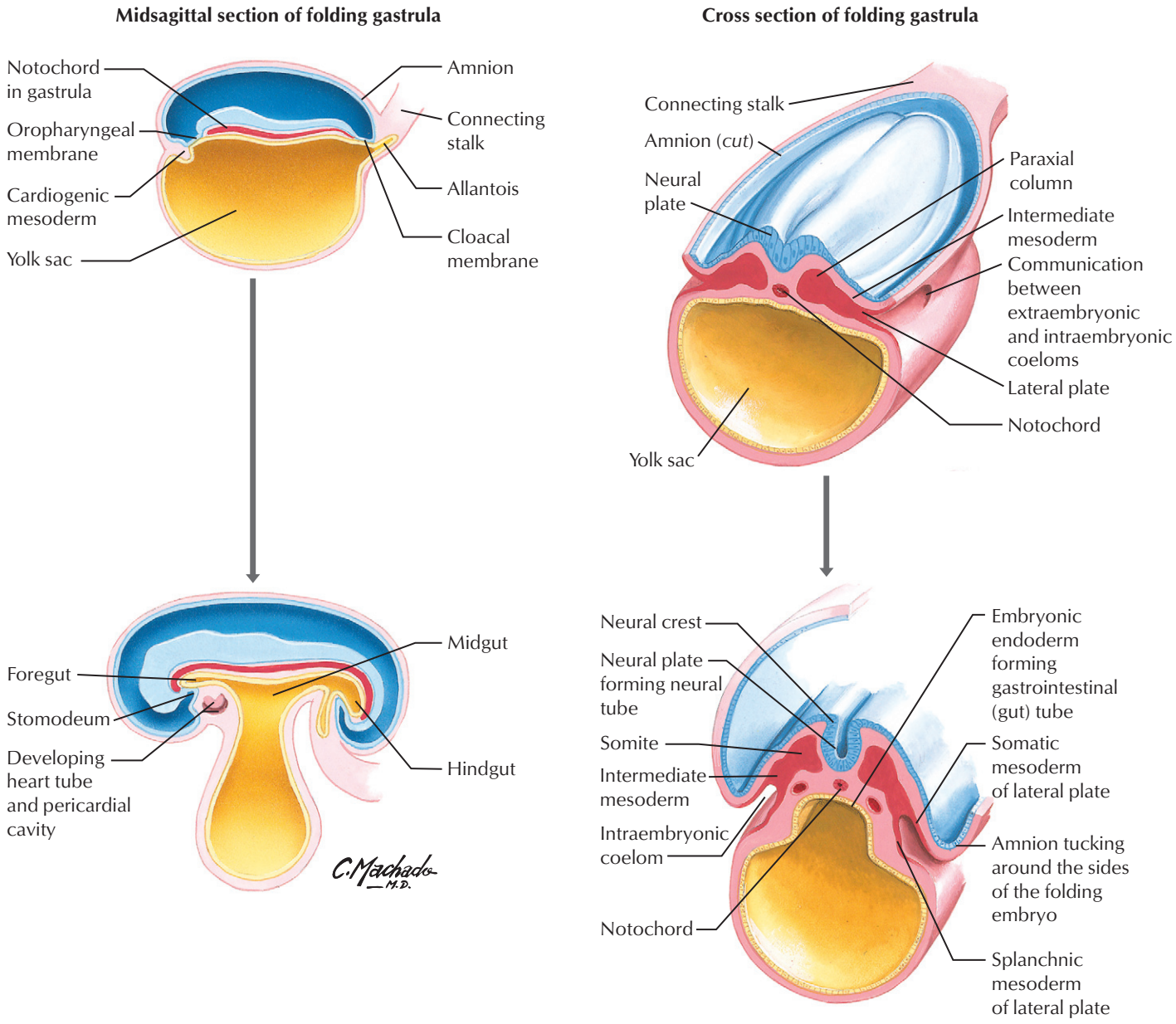
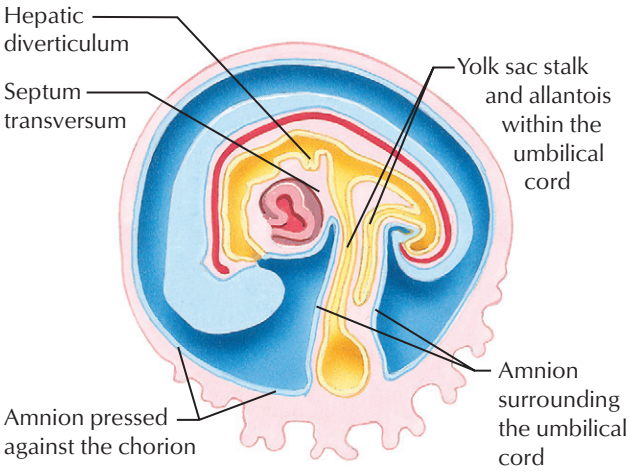
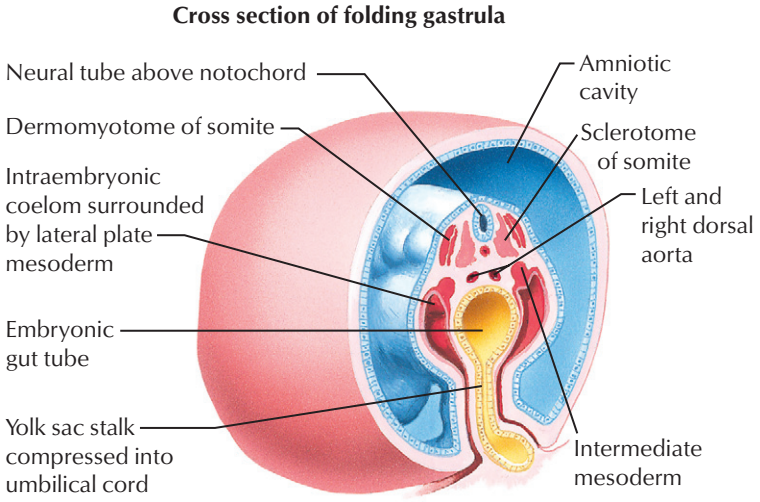


FIGURE 2.11 FOLDING OF THE GASTRULA

Shaping of the gastrula occurs as the amnion tucks around and under the elongated embryo on all sides. The endoderm of the embryo (roof of the yolk sac) is compressed into a tube by this process. The remainder of the yolk sac extends out of the embryo ventrally and is pushed against the connecting stalk by the amnion. Most of the transverse folding involves an extension of the lateral plate and enlargement of the coelom, which divides the ventral part of the embryo into gut and body wall components. The amnion also tucks around the head and tail ends of the embryo.





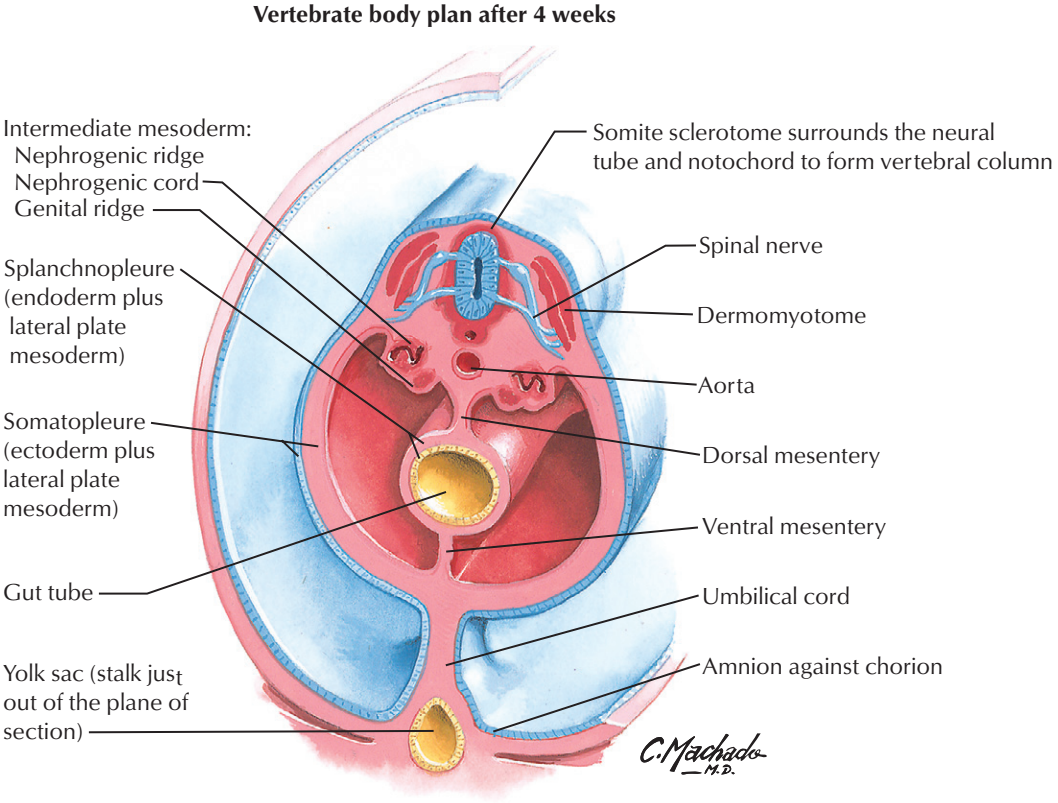
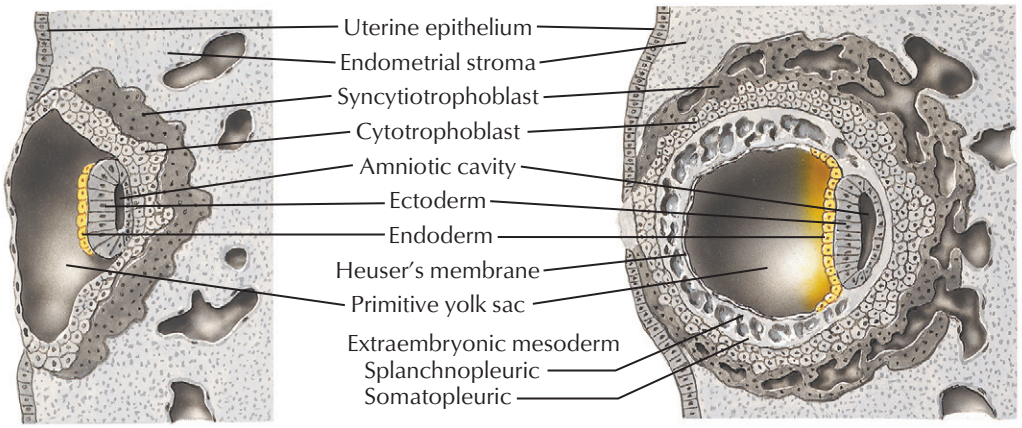
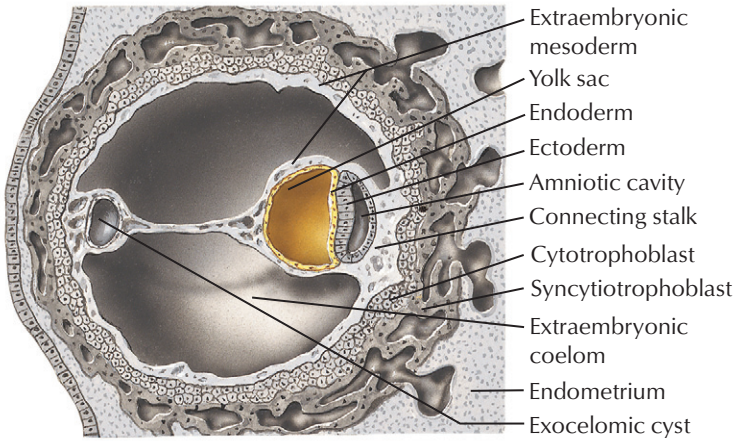


FIGURE 2.12 THE VERTEBRATE BODY PLAN

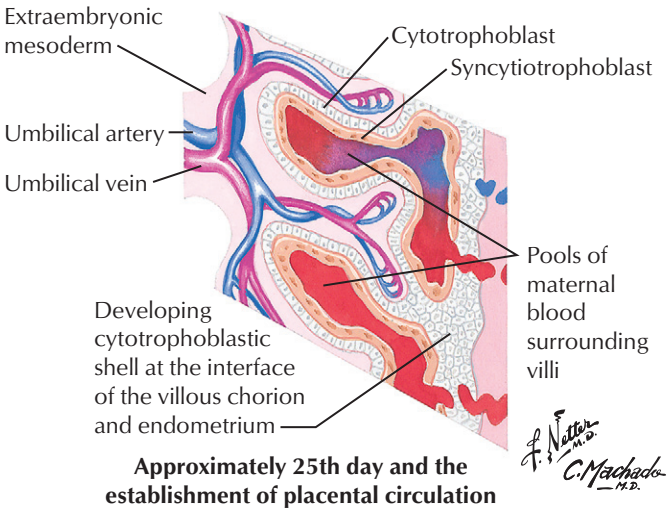
The vertebrate body plan is established after folding of the gastrula. By the end of the fourth week (bottom figure), the lateral plate is now a thin coating of the coelomic cavities. With the surface ectoderm, it forms **somatopleure,** the basis of the lateral and ventral body wall. The endoderm and mesoderm from the lateral plate form **splanchnopleure,** the primordium of the gut tube and visceral organs that develop from it. Each somite differentiates into a **myotome** that will form muscle, a **dermatome** relating to the surface ectoderm, and a bone-forming **sclerotome** that condenses around the neural tube. The somite myotomes connect with the spinal nerves, and the ventral part (hypomere) will migrate into the somatopleure.



Approximately 7½ days **Approximately 12th day**



Approximately 15th day

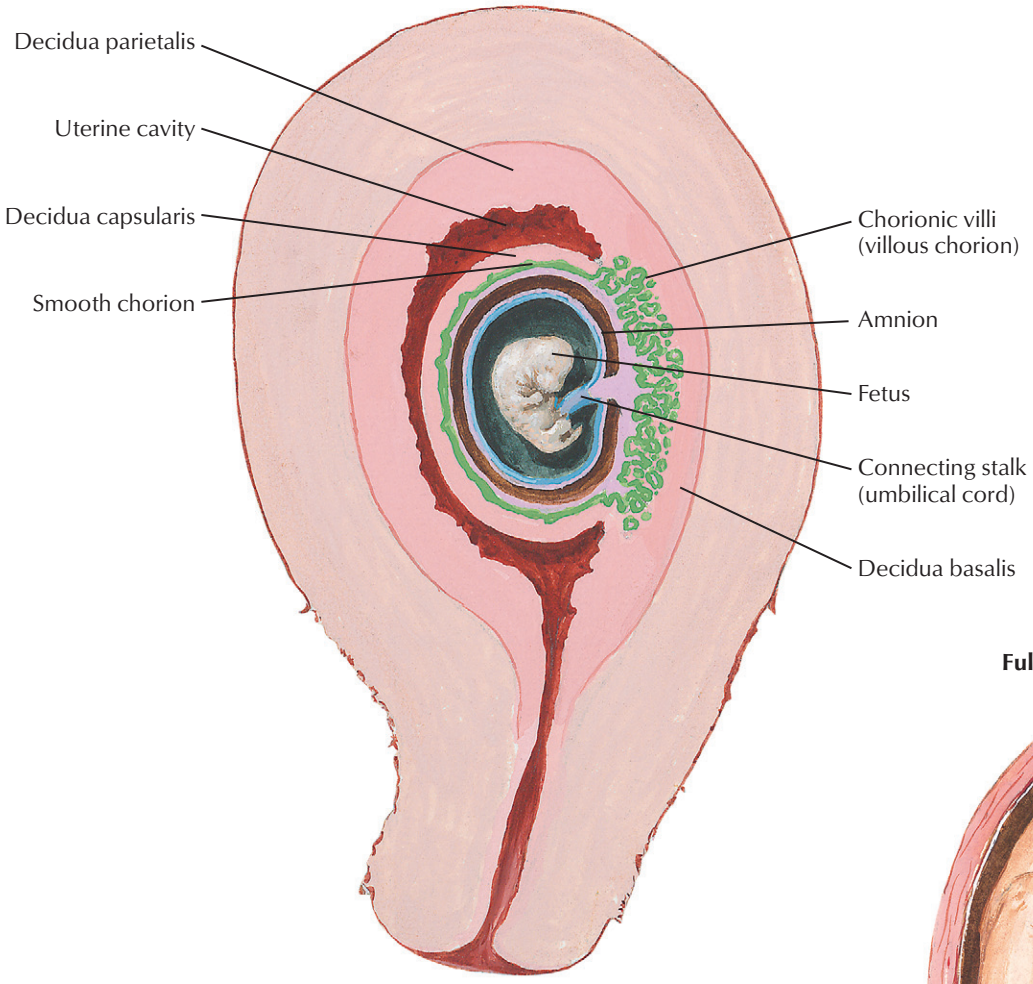


Approximately 25th day and the establishment of placental circulation

FIGURE 2.13 FORMATION OF THE PLACENTA

All three layers of the chorion invade the endometrium to form branching, finger-like **villi.** The **syncytiotrophoblast** is in direct contact with maternal blood, and the mesoderm forms the connective tissue core of the villi and their blood vessels. The **cytotrophoblast** disappears midway through pregnancy to help thin the placental membrane between fetal and maternal blood. The syncytiotrophoblast synthesizes hormones from fetal and maternal precursors. **Protein hormones** include **human chorionic gonadotropin (hCG),** human placental lactogen, human chorionic thyrotropin, and human chorionic corticotropin. hCG prevents menstruation by maintaining the corpus luteum. Placental **steroid hormones** include **progesterone and estrogens** that help the corpus luteum maintain the later stages of pregnancy.

Early fetal development and membrane formation in relation to the uterus as a whole (schematic)



Full-term fetus within the uterus

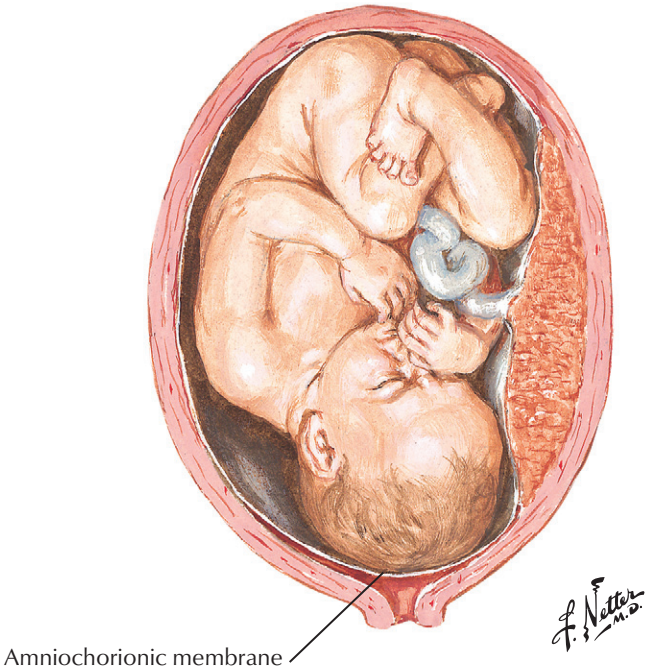


FIGURE 2.14 THE ENDOMETRIUM AND FETAL MEMBRANES

Fetal development is entirely within the decidua (mucosal wall of the uterus or endometrium). The decidua is named according to its relationship to the placenta and fetal membranes. The **decidua parietalis** is uninvolved with the fetus and placenta on the anterior uterine wall. The **decidua capsularis** is the thin layer or "capsule" of endometrium over the **smooth chorion** and amnion. The **decidua basalis** is the maternal contribution to the placenta. The **villous chorion** is the fetal component of the placenta. The decidua capsularis disappears, and the fused **amniochorionic membrane** is pressed against the decidua parietalis obliterating the uterine cavity. This membrane ruptures during labor or may cause labor if the rupture is premature.

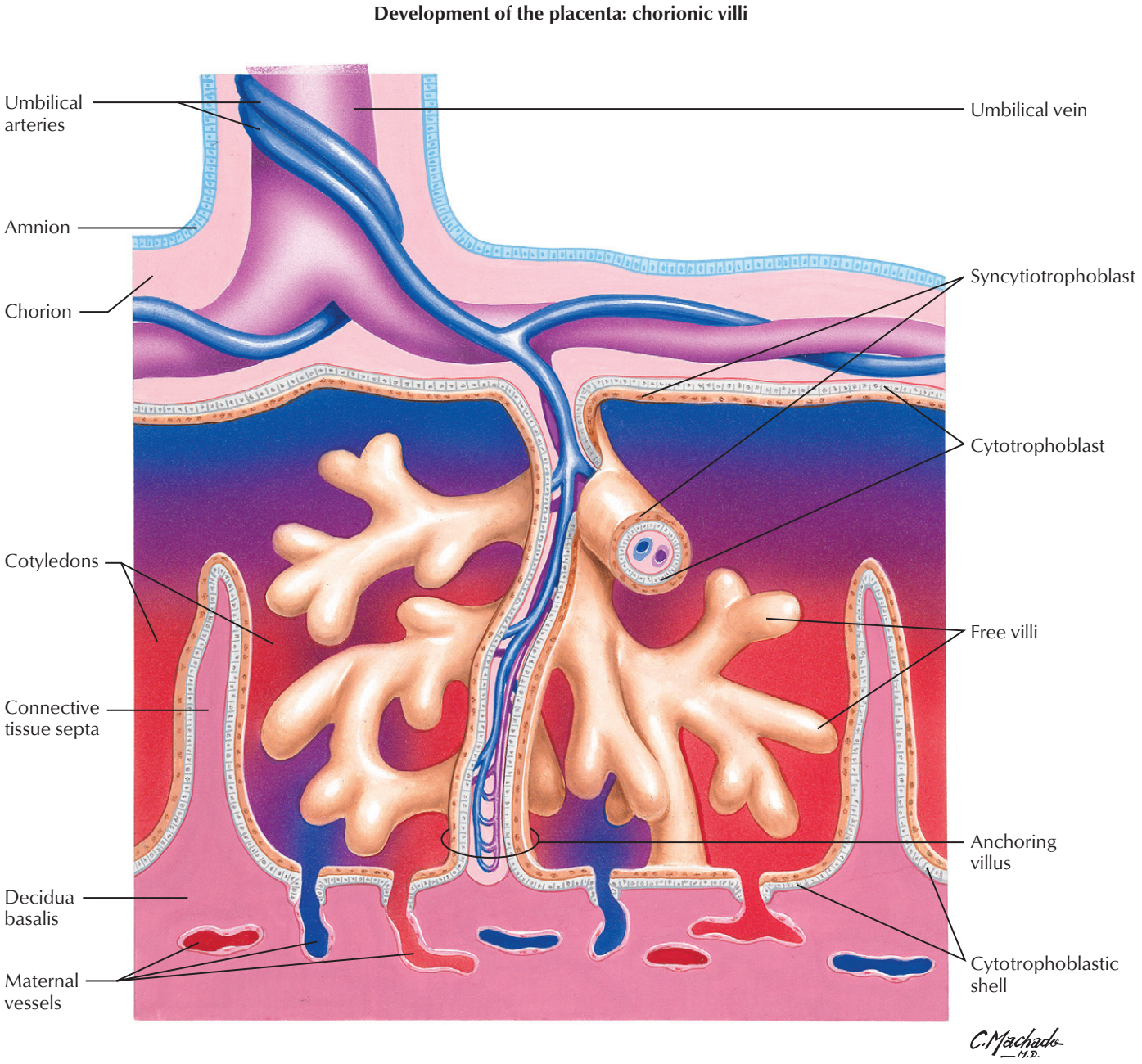
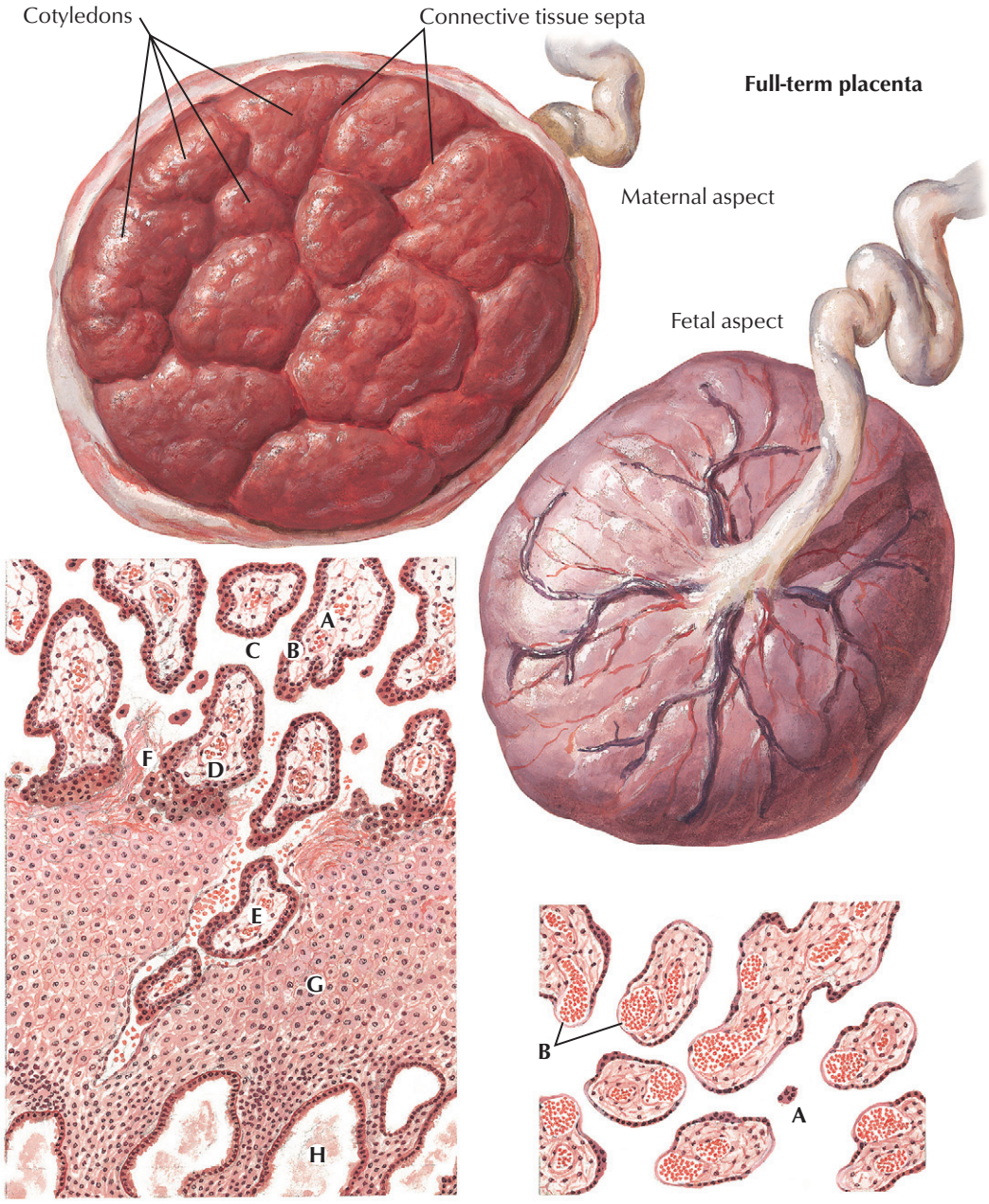


FIGURE 2.15 PLACENTAL STRUCTURE

The **chorionic plate** is on the fetal surface of the placenta. Extending from it with placental branches of the umbilical vessels are **stem villi** that branch extensively to form the free villi, where metabolic exchange occurs. The syntrophoblast is the outer layer of the villi except at the ends of the **anchoring villi** that connect the villous chorion to the decidua basalis. Here the cytotrophoblast layer extends through the syntrophoblast to form the **cytotrophoblastic shell** at the interface between fetal and maternal components of the placenta. Decidual spiral arteries open through this shell to directly bathe the chorionic villi in maternal blood. The placental membrane (formerly the "maternal-fetal blood barrier") separating maternal and fetal blood consists of the following components early in pregnancy: syncytiotrophoblast, cytotrophoblast, villi mesenchyme, fetal blood vessel epithelium and its basal lamina. The placental membrane thins in later pregnancy by the elimination of the cytotrophoblast and the pressing of fetal blood vessels against the syntrophoblast, where they share a basal lamina. This gets maternal and fetal blood as close together as possible for more efficient metabolic exchange.



Cross-section through deep portion of placenta—early gestation
(A) Villus, (B) trophoblast, (C) intervillous space, (D) anchoring villus, (E) villus invading blood vessel, (F) fibrinoid degeneration, (G) decidua basalis, (H) gland

Appearance of placental villi at term
(A) Syncytial cell mass becoming trophoblastic embolus, (B) fetal blood vessel endothelium against a thinned syncytiotrophoblast, where they share a basal lamina. The cytotrophoblast has disappeared

FIGURE 2.16 EXTERNAL PLACENTAL STRUCTURE; PLACENTAL MEMBRANE

Substances that cross the placental membrane:

Beneficial
Metabolic gases (O_2, CO_2)
Fetal urea, uric acid, bilirubin
Water and electrolytes
Vitamins, glucose, amino acids, free fatty acids
Fetal and maternal red blood cells (later months)
Steroid hormones
IgG immunoglobulins

Harmful
Carbon monoxide
Most viruses (including HIV, polio, measles)
Most drugs (including alcohol, cocaine, nicotine, caffeine, anesthetics, anticancer drugs)
Treponema pallidum (syphilis) and *Toxoplasma gondii* (parasite)
Anti-Rh antibodies (IgG)

Substances that do not cross the maternal-fetal blood barrier:
Most bacteria
Most proteins (cross very slowly), protein hormones, insulin
IgM immunoglobulins
Maternal triglycerides, cholesterol, and phospholipids
Some drugs (e.g., heparin, curare, methyl-dopa)

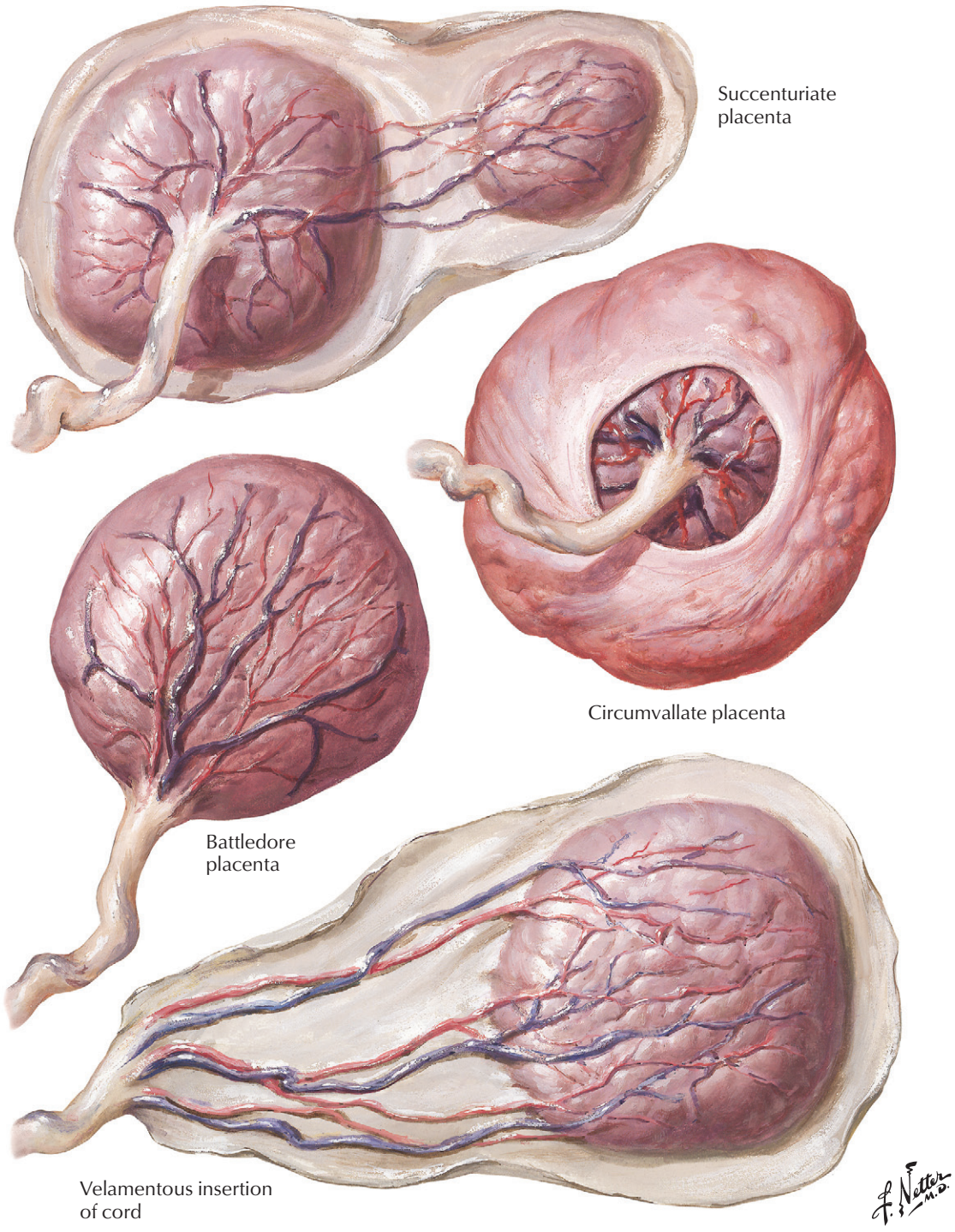


FIGURE 2.17 PLACENTAL VARIATIONS

A placenta can have accessory lobes with vascular connections between them (succenturiate placenta), or there can be no vascular connections (placenta spuria—not shown). The umbilical cord may be inserted at the margin of the placenta to give it a clublike appearance (battledore placenta). In a more extreme type of marginal insertion, the umbilical cord is attached to the chorion and amnion instead of the placenta (velamentous insertion of cord), and the vessels branch between the membranes before they extend over the placenta. In a circumvallate placenta, the membranes extend over the placenta to form a ring before doubling back toward the margin. Most variations are of no consequence, although velamentous insertion of the cord can result in serious bleeding.

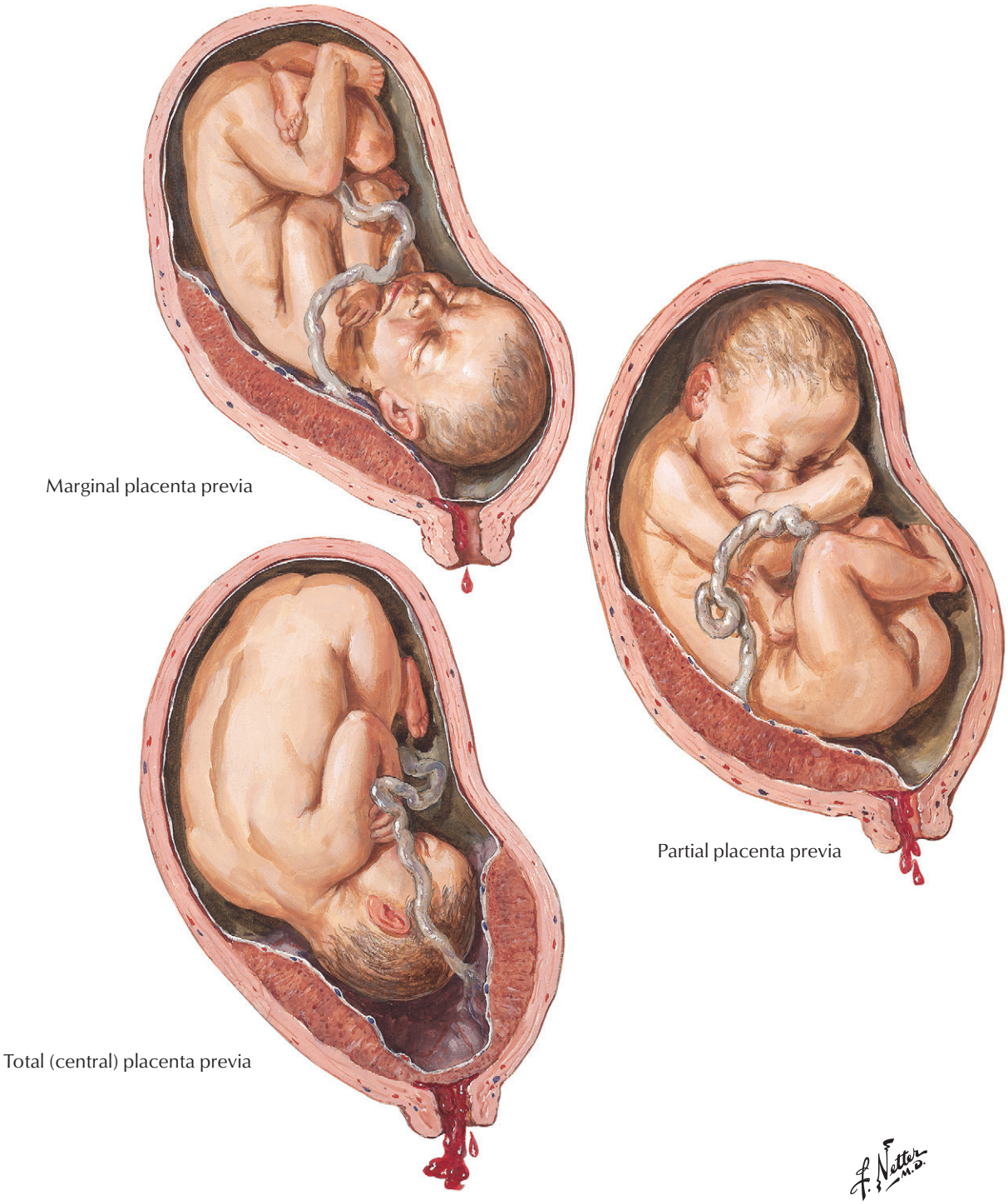
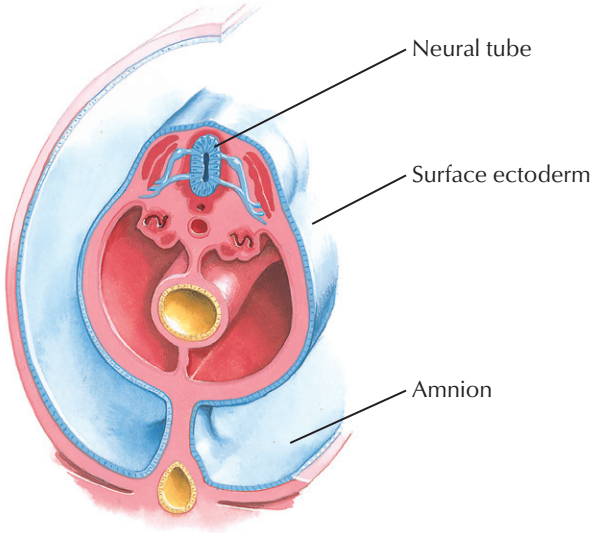
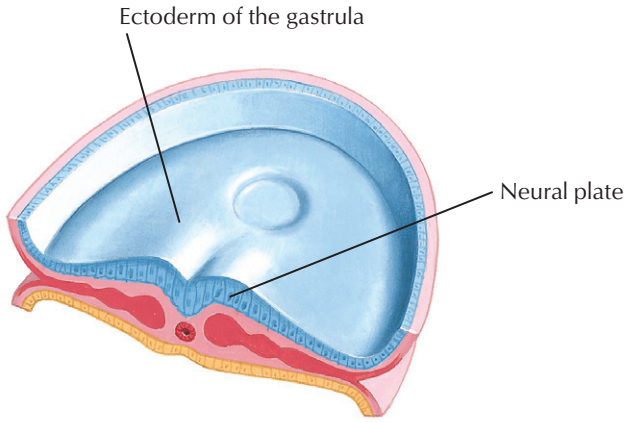


FIGURE 2.18 PLACENTA PREVIA

If implantation is in the lower part of the uterus, the placenta will partially or totally cover the internal os of the cervix. It can block the birth canal and is a common cause of bleeding in the third trimester. Hemorrhage from placenta previa can be fatal to the fetus or even the mother.





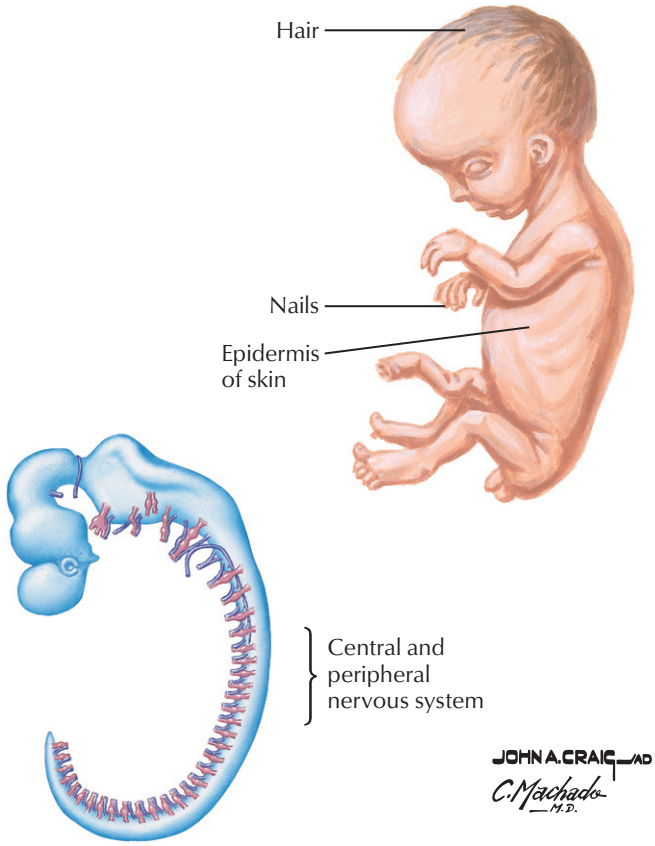
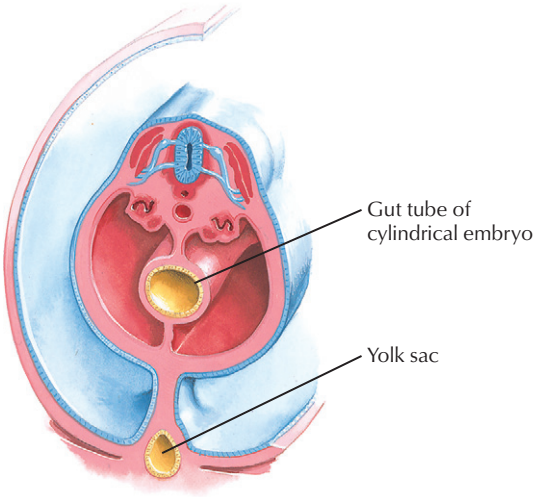


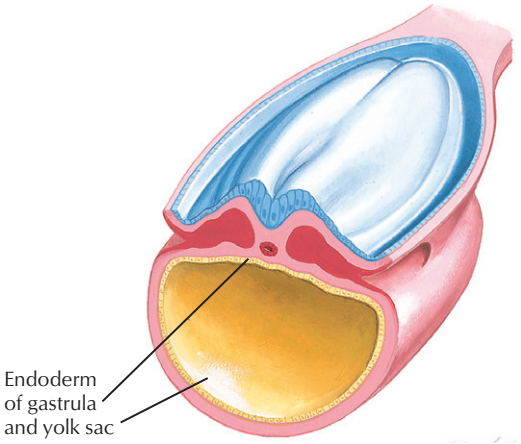
CHART 2.1 ECTODERMAL DERIVATIVES

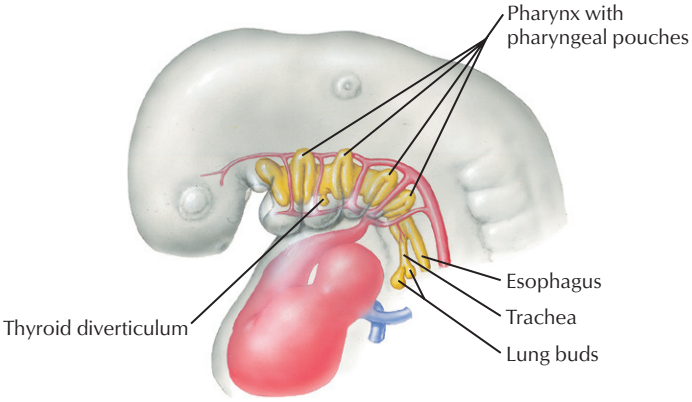
Primordia	Derivatives or Fate
Surface ectoderm	Epidermis of the skin
	Sweat, sebaceous, and mammary glands
	Nails and hair
	Tooth enamel
	Lacrimal glands
	Conjunctiva
	External auditory meatus
(Stomodeum and nasal placodes)	Oral and nasal epithelium
	Anterior pituitary
(Otic placodes)	Inner ear
(Lens placodes)	Lens of eye
Neural tube	Central nervous system
	Somatomotor neurons
	Branchiomotor neurons
	Presynaptic autonomic neurons
	Retina/optic nerves
	Posterior pituitary
Neural crest	Peripheral sensory neurons
	Postsynaptic autonomic neurons
	All ganglia
	Adrenal medulla cells
	Melanocytes
	Bone, muscle, and connective tissue in the head and neck
Amnion	Protective bag (with chorion) around fetus

FIGURE 2.19 SUMMARY OF ECTODERMAL DERIVATIVES

Ectoderm gives rise to the nervous system and the outer covering of the body. It forms the epithelial component of the skin—the epidermis—and all of the glands, continuations, invaginations, and structures that develop from it. Hair and nails consist of protein-filled ("keratinized") cells that are similar in composition to the keratinized layer of squamous cells on the surface of the epidermis. Placodes are thickenings of surface ectoderm in the head, and the stomodeum is an invagination of ectoderm that lines the oral cavity. An unusual fate of ectoderm is the formation of connective tissue and muscle from neural crest cells in the head and neck. Ectoderm and all other cells and tissues in the body originally come from the embryonic epiblast.







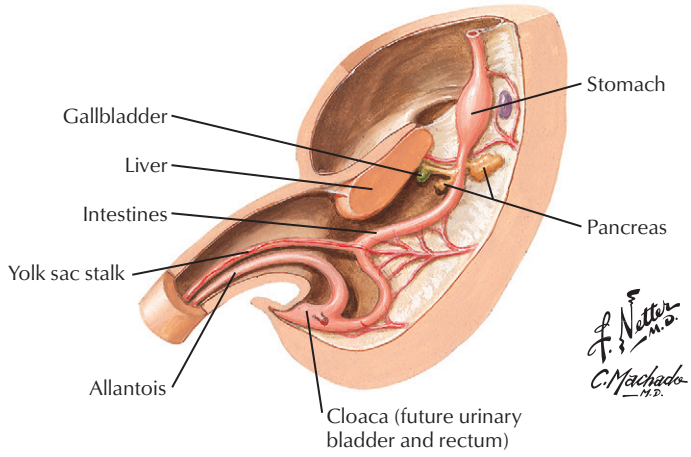


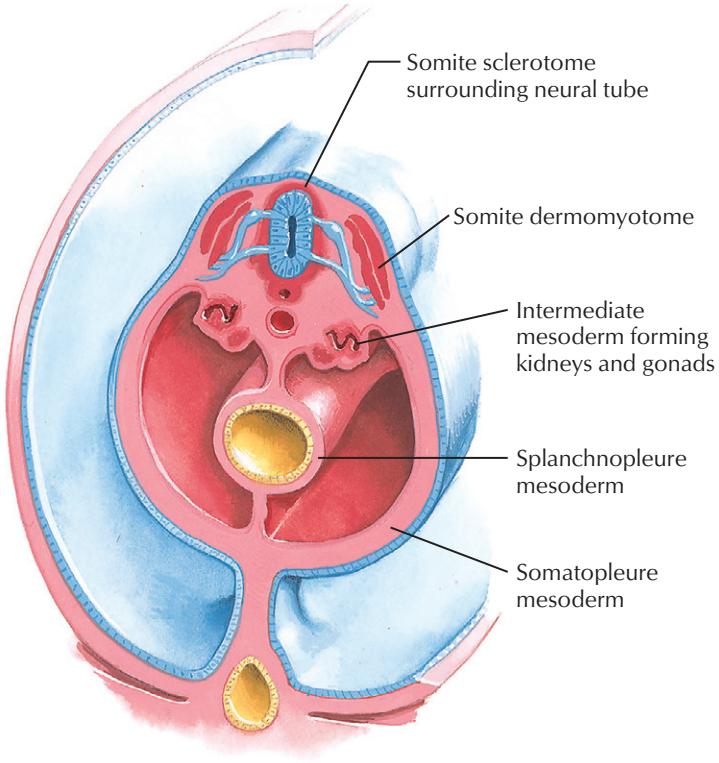
CHART 2.2 ENDODERMAL DERIVATIVES

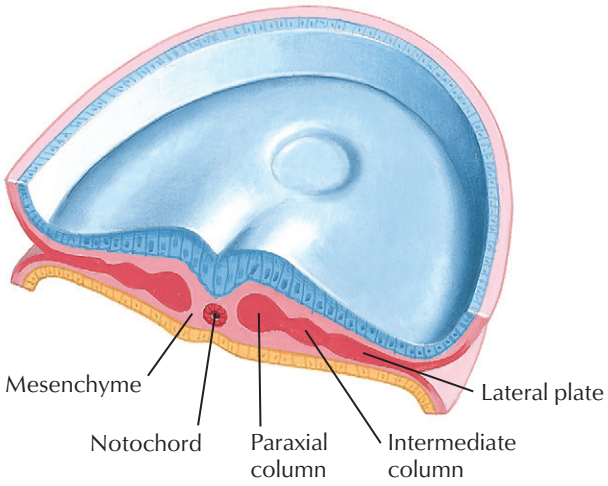
Primordia	Epithelial Derivatives or Fate
Gut tube endoderm	GI tract (enterocytes) Mucosal glands of GI tract Parenchyma of GI organs (liver, pancreas) Airway lining (larynx, trachea, bronchial tree) Thyroid gland Tonsils
Cloaca (part of hindgut)	Rectum and anal canal Bladder, urethra, and related glands Vestibule Lower vagina
Pharyngeal pouches (part of foregut)	Auditory tube and middle ear epithelium Palatine tonsil crypts Thymus gland Parathyroid glands C cells of the thyroid gland
Yolk sac	Embryonic blood cell production (mesoderm) Pressed into umbilical cord, then disappears
Allantois (from yolk sac, then cloaca)	Embryonic blood cell production (mesoderm) Vestigial, fibrous urachus Umbilical cord part disappears

GI, Gastrointestinal.

FIGURE 2.20 SUMMARY OF ENDODERMAL DERIVATIVES

Endoderm is derived from the embryonic epiblast in a wave of cellular migration that displaces the hypoblast. After folding of the gastrula into a cylinder, the endoderm is shaped into an epithelial, gastrointestinal tube extending from the stomodeum to the cloacal membrane. Most internal glands and organs develop as buds or evaginations of the endodermal tube (e.g., thyroid gland, liver, pancreas) or from the tube itself (e.g., stomach, intestines). The simple cuboidal endoderm gives rise to the epithelial linings (parenchyma) of these organs. Included is the lining of the airway—the larynx, trachea, and bronchial tree.





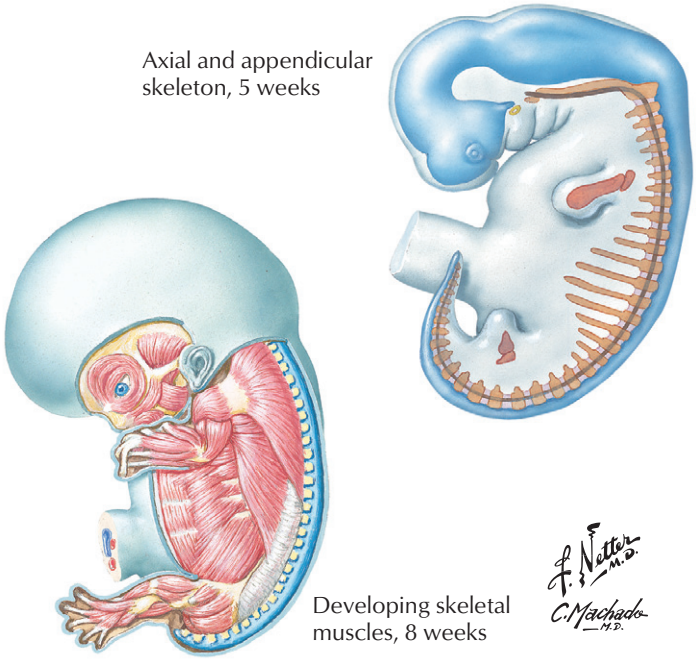


CHART 2.3 MESODERMAL DERIVATIVES

Primordia	Derivatives or Fate
Notochord	Nucleus pulposus of an intervertebral disc Induces neurulation
Paraxial columns (somites)	Skeletal muscle Bone Connective tissue (e.g., dorsal dermis, dura mater)
Intermediate mesoderm	Gonads Kidneys and ureters Uterus and uterine tubes Upper vagina Ductus deferens, epididymis, and related tubules Seminal vesicles and ejaculatory ducts
Lateral plate mesoderm	Dermis (ventral) Superficial fascia and related tissues (ventral) Bones and connective tissues of limbs Pleura and peritoneum GI tract connective tissue stroma
Cardiogenic mesoderm	Heart Pericardium

GI, Gastrointestinal.

FIGURE 2.21 SUMMARY OF MESODERMAL DERIVATIVES

Mesoderm originates from the ectoderm of the primitive streak and primitive node during gastrulation. Cardiogenic mesoderm is also from the primitive streak—the heart and pericardium have no endodermal contributions. Mesoderm is in the form of dense, cellular, craniocaudal columns surrounded by loose embryonic connective tissue (mesenchyme). They give rise to bone, muscle, connective tissue, urogenital organs, and the pleural and peritoneal linings of the body cavities. The head is not well developed at the time of gastrulation, so most of the mesoderm in the head and neck comes from the ectodermal neural crest instead of the mesodermal columns (with the exception of somites that do extend into the head).

Terminology

Allantois	The fourth extraembryonic membrane that extends from the yolk sac into the connecting stalk (future umbilical cord), then shifts to the hindgut cloaca. With the yolk sac, it is the first source of embryonic blood cells in mammals. In egg-laying animals, it lines the inner surface of the egg for gas exchange.
Chorion	Extraembryonic membrane derived from the trophoblast of the blastocyst. The smooth chorion and amnion surround the fetus as its protective "bag." The villous chorion is the fetal component of the placenta.
Chorionic plate	The chorionic membrane on the fetal surface of the placenta that gives rise to the stem villi. The umbilical vessels extend from the umbilical cord to the villi through the chorionic plate.
Corpus luteum	(L., "yellow body") The endocrine gland in the ovary that is formed from a follicle after release of the ovum at ovulation. It produces progesterone (and estrogen) to prepare the endometrium for pregnancy. If pregnancy does not occur, it degenerates into a corpus albicans ("white body") that eventually disappears.
Cotyledons	(G., "a cup-shaped hollow") Irregularly shaped lobes visible on the maternal surface of the placenta circumscribed by deep clefts and decidual septa.
Cytotrophoblastic shell	The cellular plate that attaches the chorionic villi of the placenta to the decidua basalis of the endometrium. It is derived from cytotrophoblast cells that migrate through the external syntrophoblast layer at the maternal ends of anchoring villi.
Decidual reaction	Reaction of maternal connective tissue cells in the decidua basalis to implantation. They swell with glycogen and lipid and produce immunosuppressive molecules to prevent a maternal immune reaction to the conceptus-derived cytotrophoblastic shell of the placenta.
Ectopic	(G., "displaced") A general term for an organ or structure that ends up in an abnormal location. An ectopic pregnancy results from abnormal implantation sites (e.g., uterine tubes, abdominal cavity).
Epiblast	Columnar cells of the inner cell mass of the blastocyst that constitute the primary ectoderm.
Endometrium	(G., "inside of the uterus") The mucosa of the uterus consisting of simple columnar epithelium and very cellular, loose connective tissue with simple tubular glands. Also called decidua (L., "falling off") because much of the mucosa is shed during menstruation.
Exocoelomic cyst	The remnant of the primary yolk sac (Heuser's membrane) that is displaced by a second wave of endodermal cell migration from the hypoblast that forms the definitive yolk sac.
Extraembryonic	The tissues and structures that are outside the embryo. These mostly consist of the extraembryonic membranes: chorion, amnion, yolk sac, and allantois.
Extraembryonic mesoderm	The mesoderm that appears between the primary yolk sac and cytotrophoblast then cavitates to line the old blastocyst cavity and complete extraembryonic membrane formation. Its origin is controversial. Various studies have it derived from the cytotrophoblast, yolk sac, or epiblast.
Fimbriae	(L., "fringe") Finger-like projections at the end of the uterine tubes that envelop the ovary at the time of ovulation and sweep the ovum into the ostium of the uterine tube.
Follicle (ovarian)	An ovarian follicle is a fluid-filled, cellular envelope surrounding an ovum that enlarges and moves to the surface of the ovary in preparation for ovulation. It is supportive and nutritive for the egg and secretes hormones.

Terminology, cont'd

Gastrulation	The production of intraembryonic mesoderm in the third week that makes the bilaminar embryonic disc a trilaminar disc (gastrula).
Heuser's (exocoelomic) membrane	The primary yolk sac formed as endodermal cells migrate to line the inner surface of the cytotrophoblast with a layer of simple squamous epithelium.
Hypoblast	Simple cuboidal epithelium of the inner cell mass of the blastocyst that constitutes the primary endoderm. It is displaced by a second wave of migration of hypoblast cells that form the definitive yolk sac coated with extraembryonic mesoderm.
Intermediate mesoderm	Primitive streak mesoderm in the gastrula that gives rise to the gonads, kidneys, and tubules and ducts of the urogenital system. It is "intermediate" between the paraxial columns and lateral plate mesoderm.
Lithopedion	(G., "stone 1 child") A dead fetus that has become calcified or hard.
Mesoderm	(G., "middle skin") The inner tissue of the gastrula between the ectoderm and endoderm. It differentiates into two forms: mesenchyme (loose embryonic connective tissue) and the very cellular mesodermal columns (notochord, paraxial columns, intermediate mesoderm, and lateral plate). Extraembryonic mesoderm is the middle layer between the trophoblast and amnion/yolk sac.
Morula	(L., "little mulberry") A product of conception, a morula is the ball of cells 3 to 4 days after fertilization that is ready to enter the uterine cavity.
Neurenteric canal	Temporary communication of the amniotic cavity with the yolk sac cavity associated with the development of the notochord.
Notochord	Midline mesoderm originating during gastrulation from the ectodermal primitive knot (node). It induces neurulation, and its only structural derivative is the nucleus pulposus of an intervertebral disc.
Notochordal canal	The hollow center that develops in the notochordal process. It communicates with the amniotic cavity via the primitive pit in the primitive knot (node).
Notochordal plate	Mesoderm of the notochord that remains after the notochordal canal breaks open into the yolk sac cavity along its entire length to form the neurenteric canal between the amniotic and yolk sac cavities. As a result, the embryonic endoderm flanks the notochordal plate until the latter infolds to form the notochord proper that is again a solid column of mesoderm within the gastrula.
Notochordal process	The initially solid column of mesoderm originating from the primitive knot (node).
Oropharyngeal membrane	Also called the oral membrane, it is a circular area at the head end of the gastrula where the ectoderm and endoderm remain in tight contact with no intervening mesoderm. It ends up at the junction of the oral cavity and pharynx, where it breaks down. Its equivalent at the tail end of the embryo is the cloacal membrane.
Prechordal plate	Endodermal cells of the future oropharyngeal membrane at the cranial end of the bilaminar disc. It limits the cranial extension of the notochordal process mesoderm during gastrulation.
Villi (placental)	Finger-like projections of the chorion that are the structural and functional units of the placenta. Most are free villi bathed in maternal blood. They originate from large stem villi on the fetal side of the placenta. Anchoring villi extend from the stem villi to the cytotrophoblastic shell that attaches to the decidua basalis.

CHAPTER 3

THE NERVOUS SYSTEM

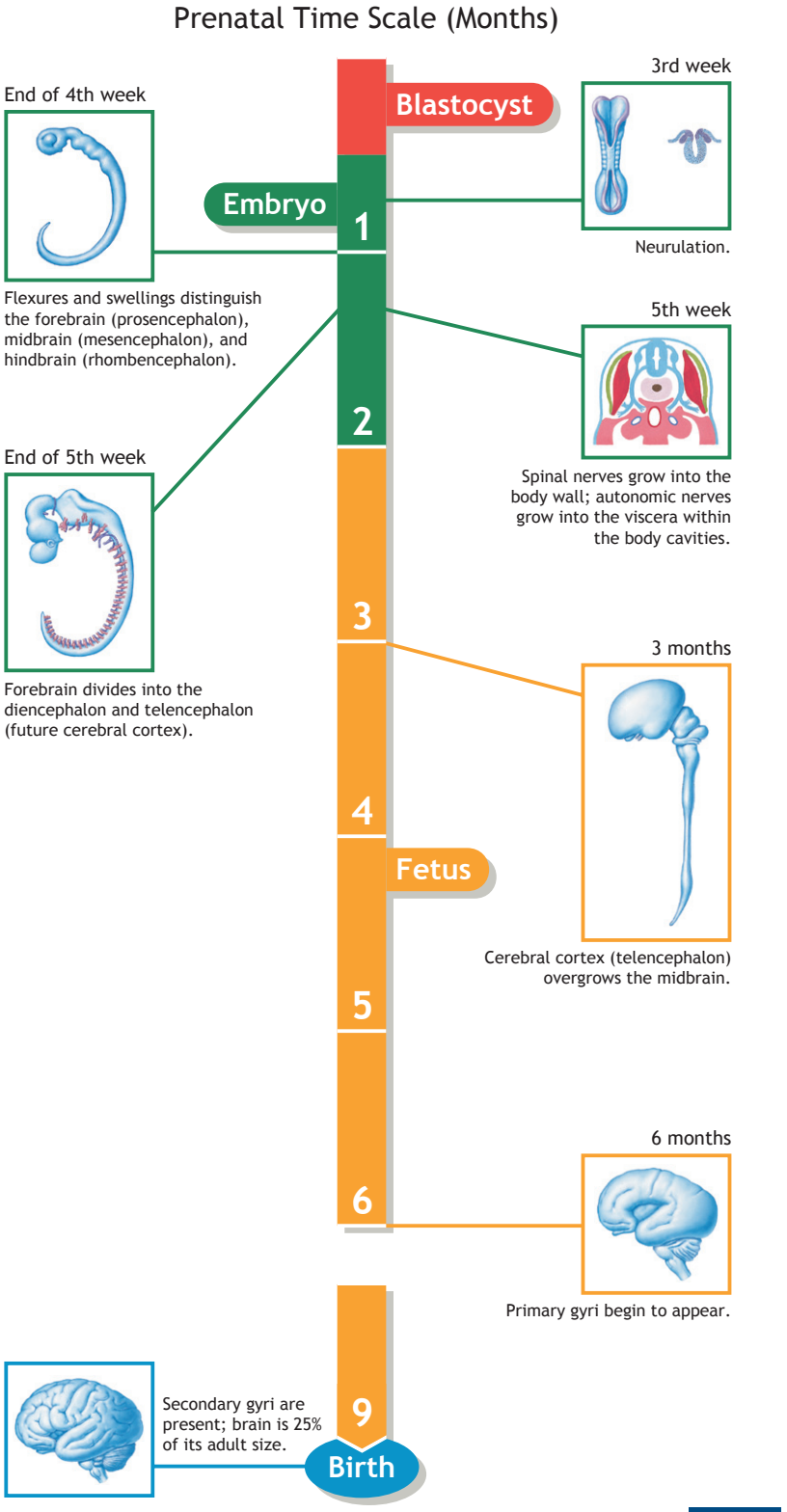
PRIMORDIA

Ectodermal neural plate, which forms the neural tube and neural crest.

PLAN

The anatomy of the adult nervous system can appear to be complex, but the pattern established in the embryo is simple and logical with a few, basic organizing principles. The dorsal half of the spinal cord and brainstem is sensory; the ventral half is motor. The 12 pairs of cranial nerves and 31 pairs of spinal nerves are mostly mixed nerves (motor and sensory) that innervate the body tissues in segmental fashion. The types and functions of the nerves are in large part related to whether they grow into somatopleure (the developing body wall) or splanchnopleure (the developing visceral compartment). The cell bodies for the motor neurons supplying skeletal muscles are located within the central nervous system (CNS); the cell bodies for sensory neurons (and postganglionic autonomic neurons) are in ganglia outside the CNS. With a few exceptions, the territoriality of the segmental peripheral nerves is retained in the adult. The nervous system may seem complex because of the absolute and differential growth of structures, plexus formation, migration of structures, nerve branching, and other phenomena, but the simple plan in the embryo is in large part retained.

TIMELINE



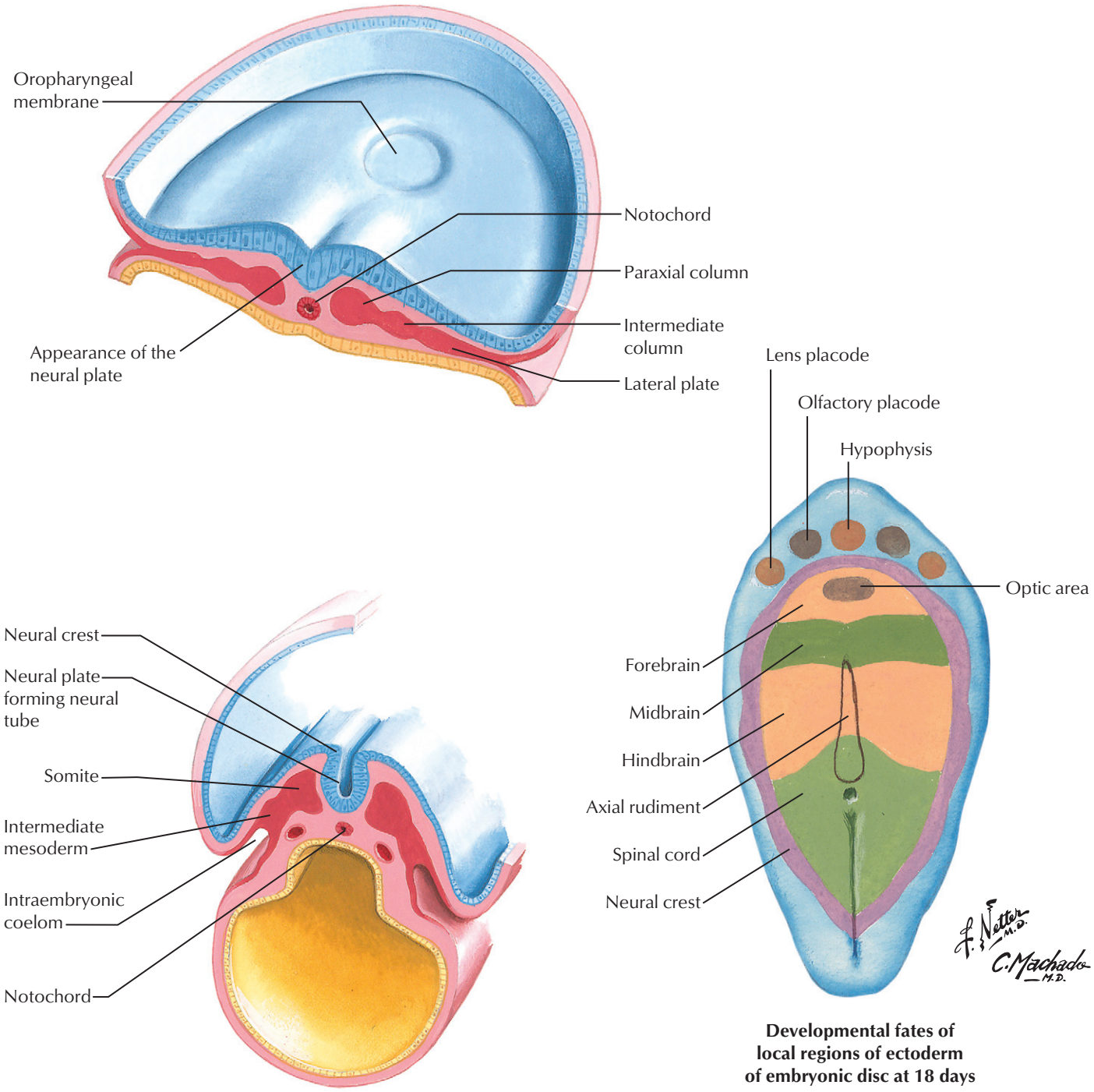


FIGURE 3.1 FORMATION OF THE NEURAL PLATE

As the primitive streak recedes toward the tail of the embryo near the end of gastrulation, the mesodermal notochord and paraxial columns begin to induce the formation of the **neural plate,** a thickening of the overlying surface ectoderm cranial to the primitive streak. Contributions of the neural ectoderm to the future brain, spinal cord, and neural crest are shown in the upper right. Because of the way the neural plate invaginates to form the neural tube, the dorsal, sensory components of the tube are lateral on the neural plate, and the ventral, motor components of the tube are medial.

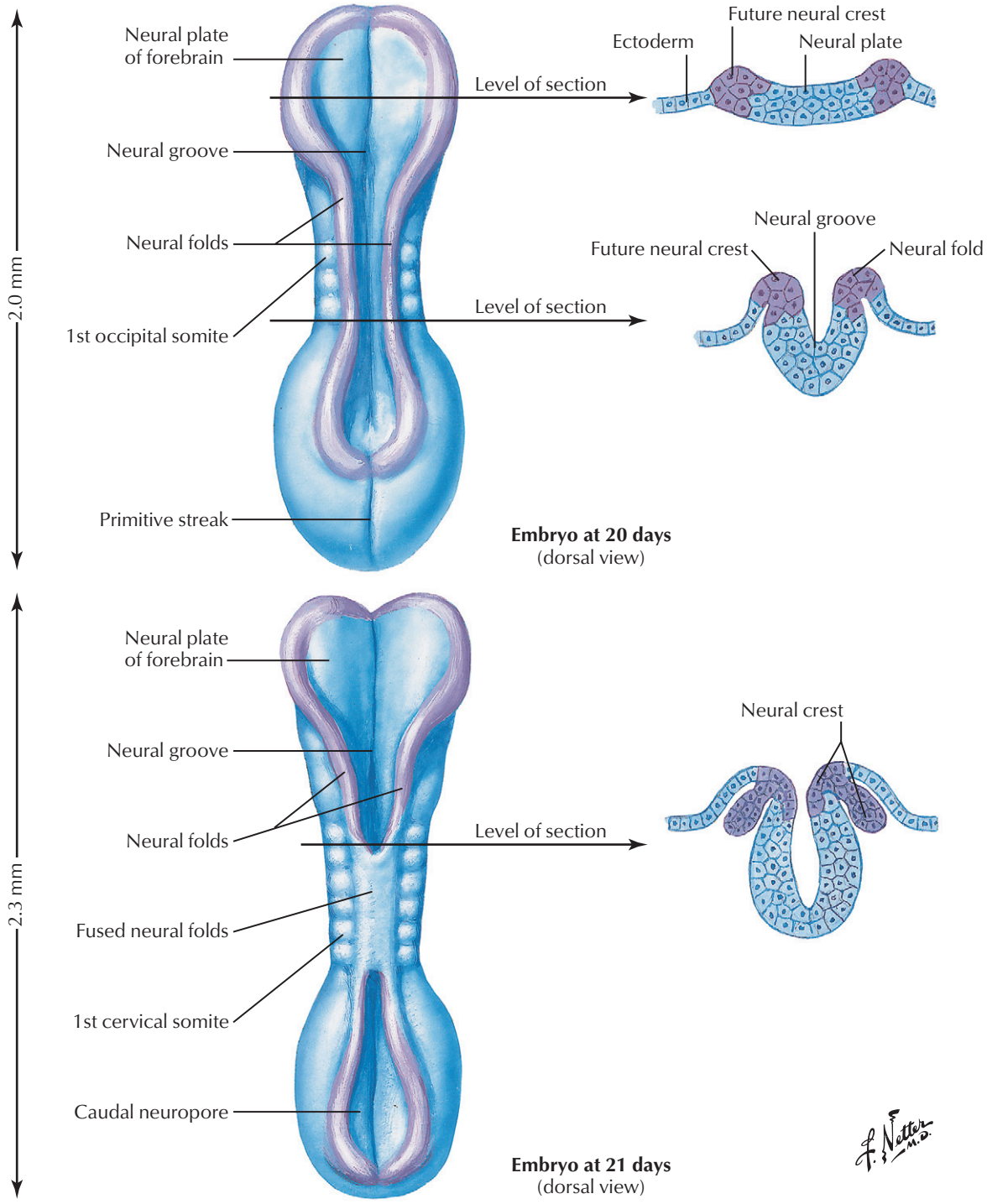


FIGURE 3.2 NEURULATION

In response to induction by the notochord and paraxial mesoderm, the surface ectoderm thickens and begins to sink and fold in on itself near the junction of the future brain and spinal cord in the middle of the embryo. The ectodermal neural crests on each side approach each other and fuse as the tube sinks below the surface. Some of these cells will pinch off and migrate to form ganglia throughout the trunk and a variety of other tissues in the head and neck. Neurulation advances both cranially and caudally. In many mammals, particularly in species with large tails, there is a secondary neurulation of midline primitive streak mesoderm in the sacral/coccygeal region beyond the caudal neuropore. The mesenchyme condenses, forms a central canal, and connects with the caudal neural tube. Abnormal secondary neurulation may contribute to tethered cord syndrome, an abnormally low positioning of the inferior portion of the spinal cord below L1.

The **neural tube** will form the brain and spinal cord, the two components of the **central nervous system (CNS).** The **neural crest** will give rise to all of the neurons whose cell bodies are located outside the CNS in the **peripheral nervous system (PNS)** of nerves, ganglia, and plexuses.

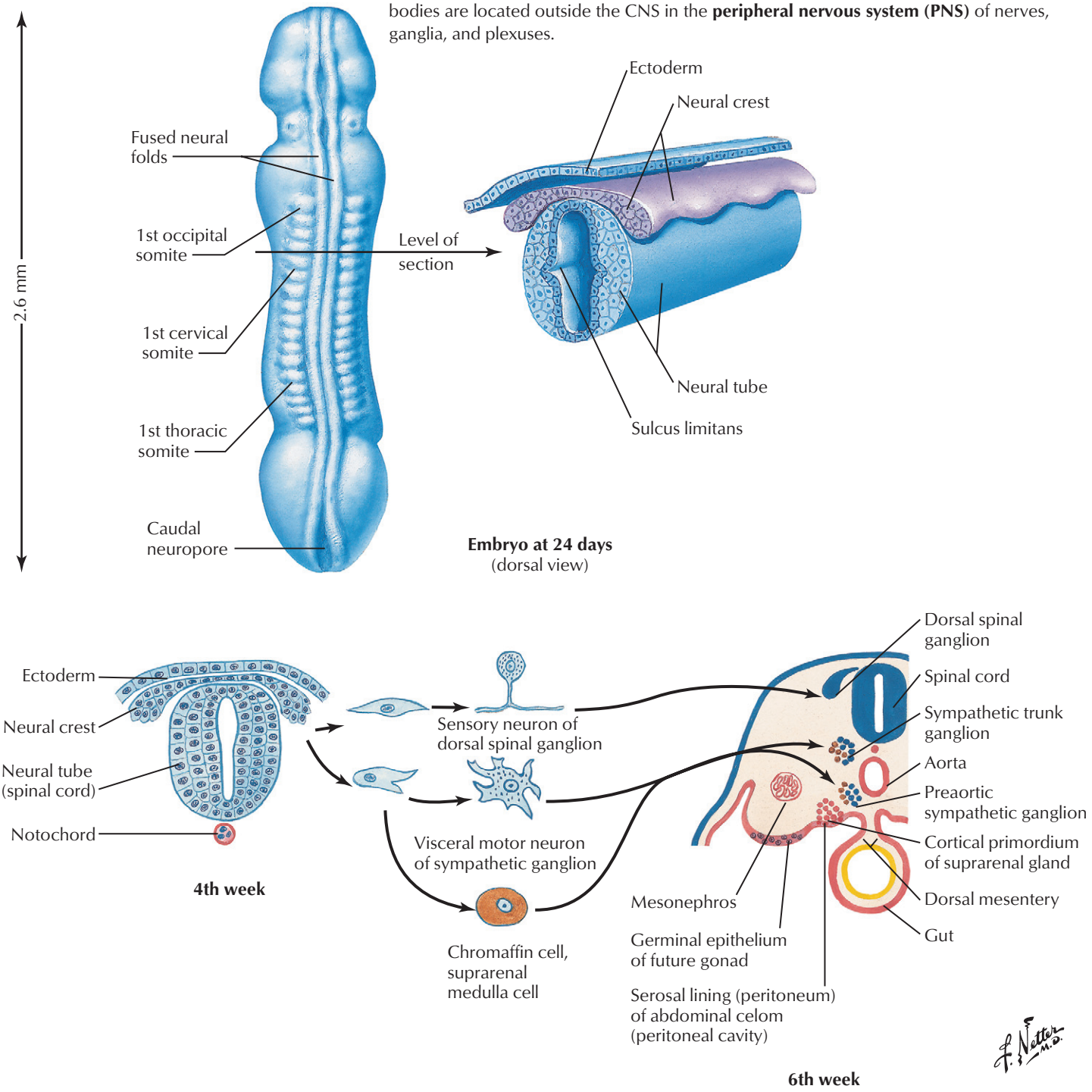


FIGURE 3.3 NEURAL TUBE AND NEURAL CREST

Derivatives of the neural tube include:

- Neurons of the CNS
- Supporting cells of the CNS
- Somatomotor neurons of the PNS
- Presynaptic autonomic neurons of PNS

Derivatives of the neural crest include:

- Sensory neurons in the PNS
- Postsynaptic autonomic neurons
- Schwann (neurilemma) cells
- Adrenal medulla cells
- Head mesenchyme
- Melanocytes in the skin
- Arachnoid and pia mater of meninges (dura mater from mesoderm)

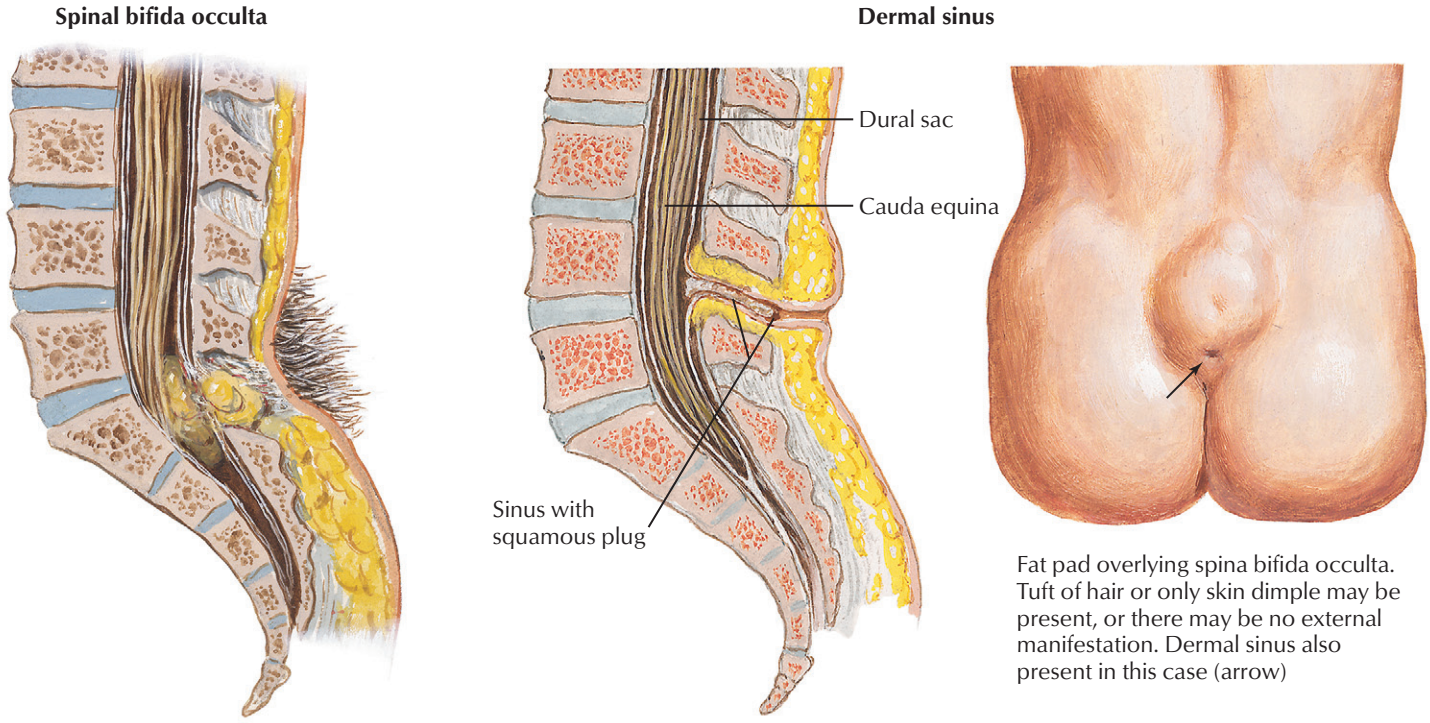


FIGURE 3.4 DEFECTS OF THE SPINAL CORD AND VERTEBRAL COLUMN

Many nervous system defects occur when the neural tube fails to develop properly. **Spina bifida** is an incomplete vertebral arch that results when the neural tube fails to sink completely below the surface, and somite sclerotome cells cannot migrate over it to complete the vertebral arch. The spinal cord may be exposed on the surface with severe functional deficits (myeloschisis); it may be completely normal in function with few visible manifestations **(spina bifida occulta),** or there may be a variety of intermediate conditions. In **meningocele,** the spinal cord is normal, but a swelling of meninges with cerebrospinal fluid projects through the defect. If part of the spinal cord is included, it is a **meningomyelocele.**

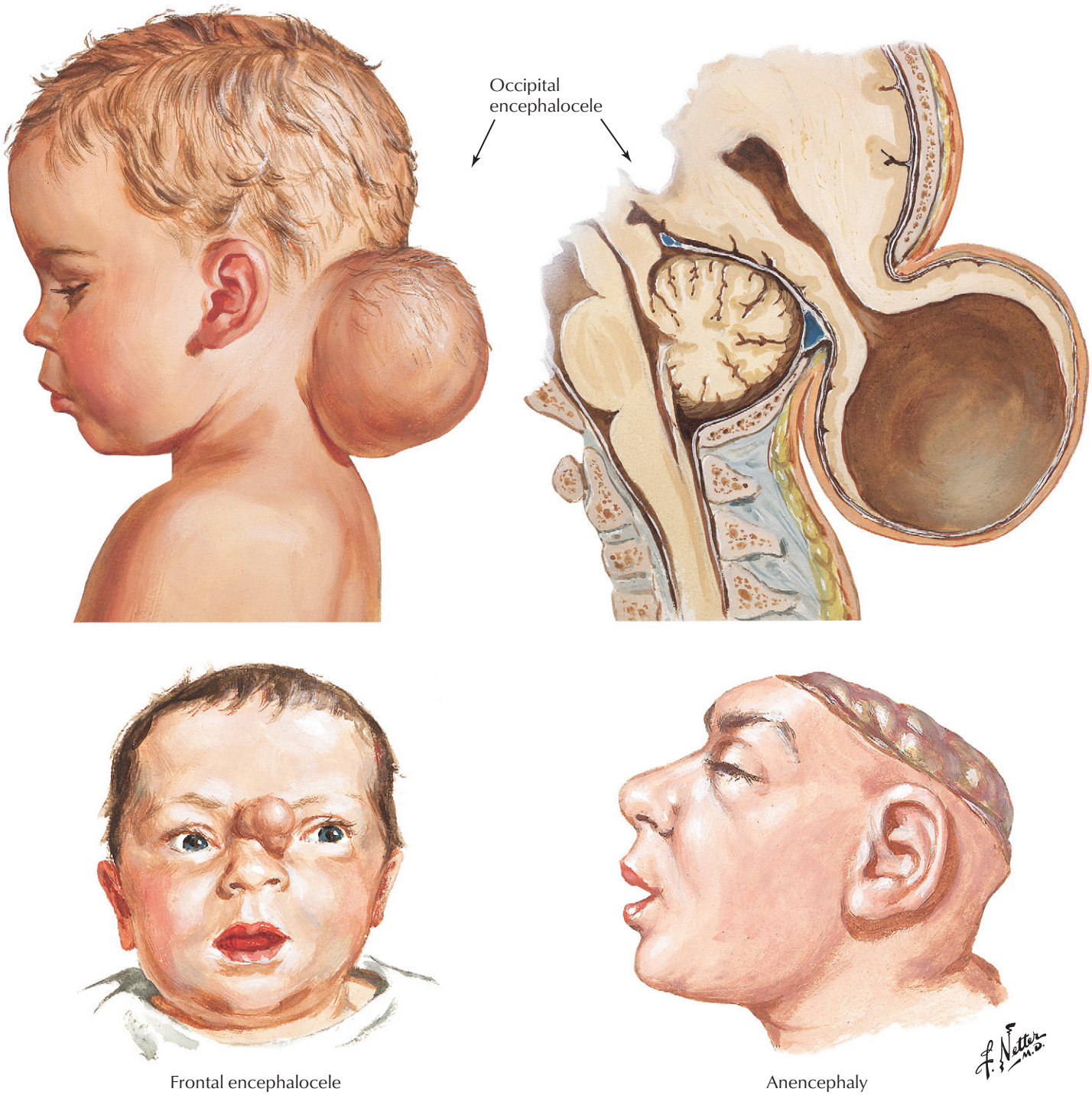


FIGURE 3.5 DEFECTS OF THE BRAIN AND SKULL

Neural tube defects in the head have effects similar to those in spina bifida, but the skull and brain are involved instead of the vertebral column and spinal cord. The occipital bone (or other midline cranial bones) may fail to ossify, and meninges project through the defect with **(encephalocele)** or without brain tissue. An extreme neural tube defect is failure of the anterior neuropore to close, resulting in absence of most of the brain and neurocranium **(anencephaly).** This is the most common major malformation in stillborn fetuses. The **Arnold-Chiari malformation** is the most common cerebellar defect (1/1000 births). Part of the cerebellum and medulla herniate through the foramen magnum, blocking the flow of cerebrospinal fluid **(communicating hydrocephalus).**

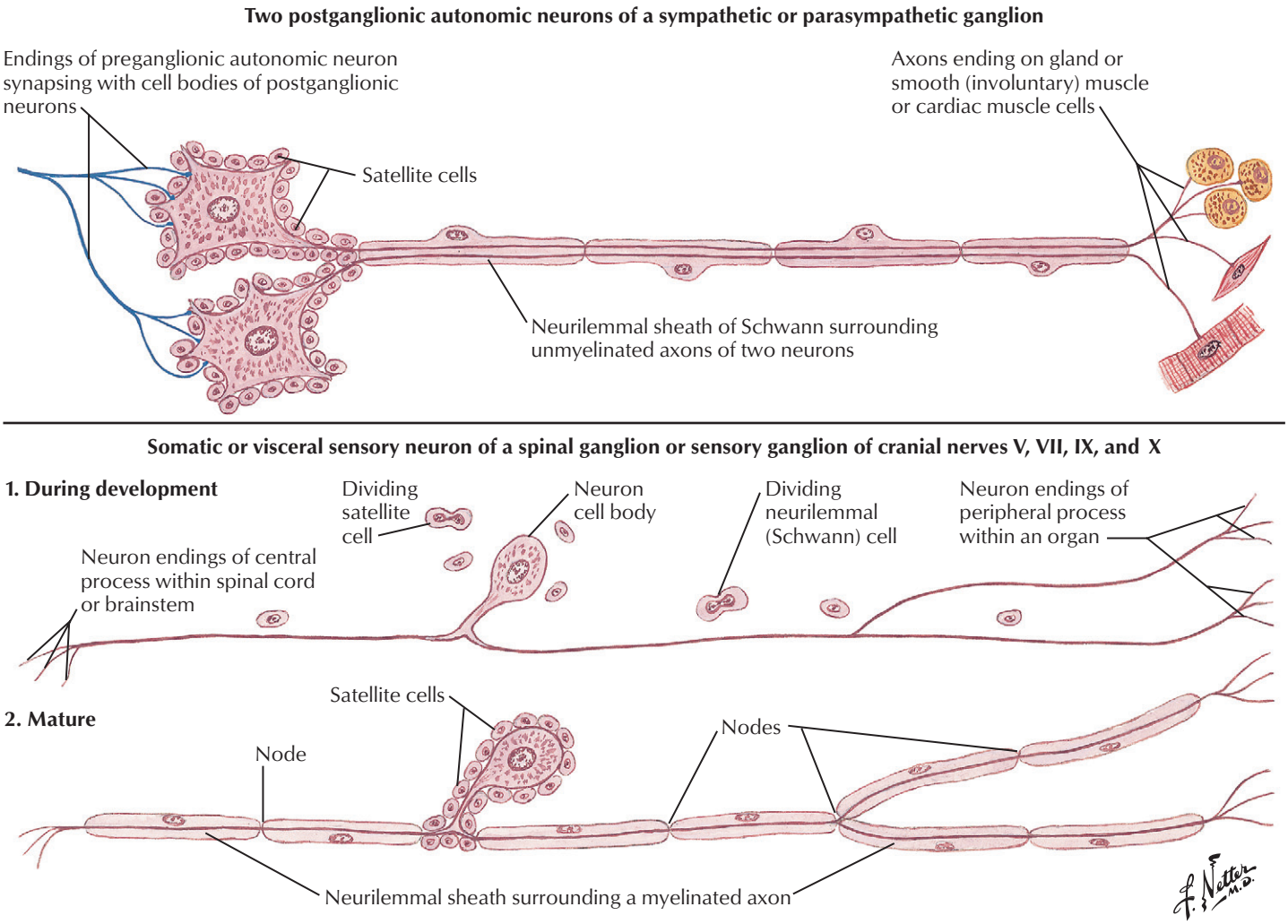


FIGURE 3.6 NEURON DEVELOPMENT

A nerve cell (fiber), or **neuron,** is the functional unit of the nervous system. Nerve cell bodies are derived from the neural tube or the neural crest. Nerve cell processes—**axons and dendrites**—sprout from the cell bodies and often grow considerable distances to the tissues and structures they innervate. The axons of motor nerves to muscles or glands grow from the CNS or autonomic ganglia; the processes from peripheral sensory neurons grow from spinal (dorsal root) and cranial ganglia to their sensory territories and into the central nervous system. A sheath of supporting cells envelops most neurons. These are termed **satellite cells** around cell bodies and **Schwann (neurilemma) cells** around the peripheral cell processes in nerves.

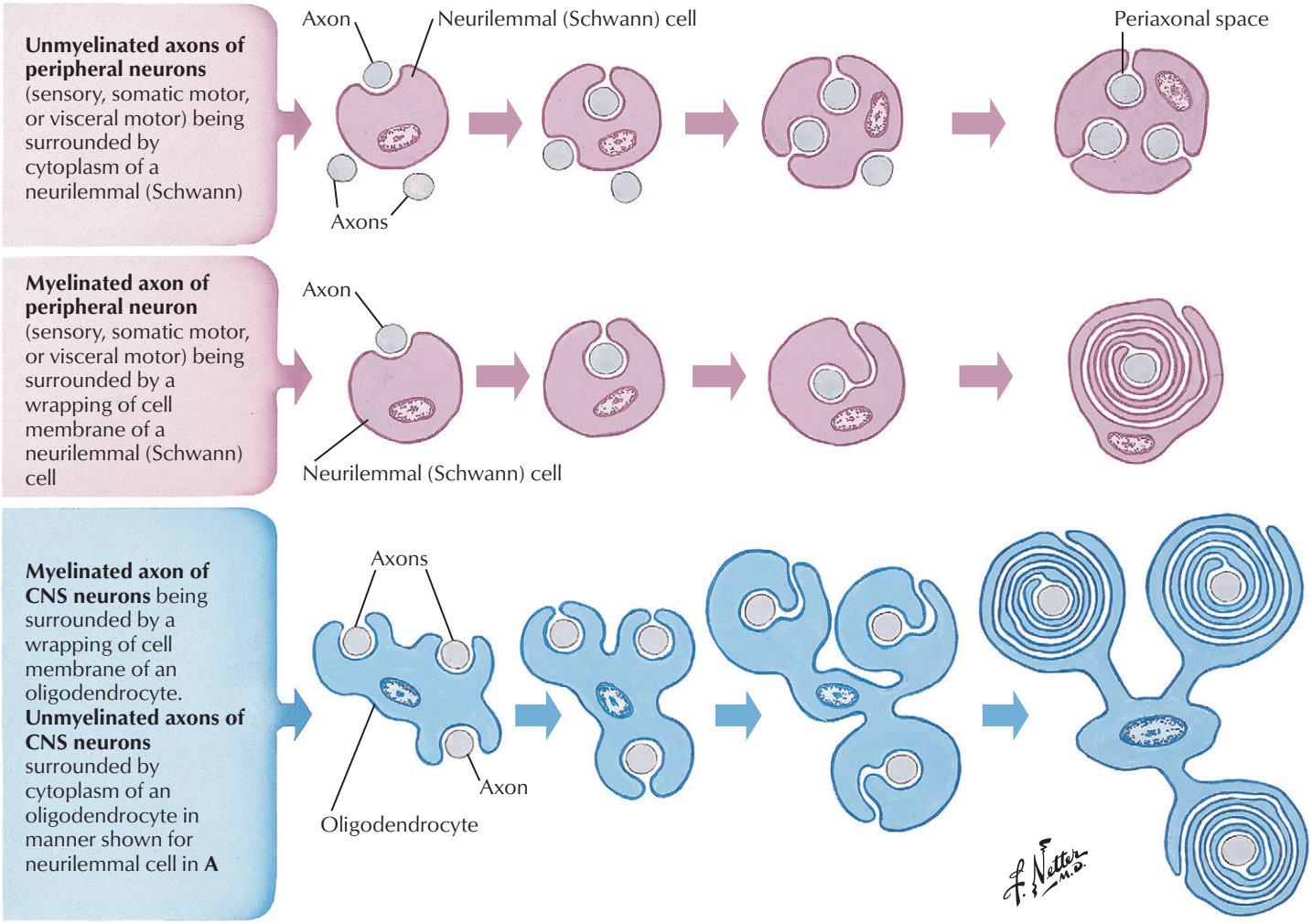
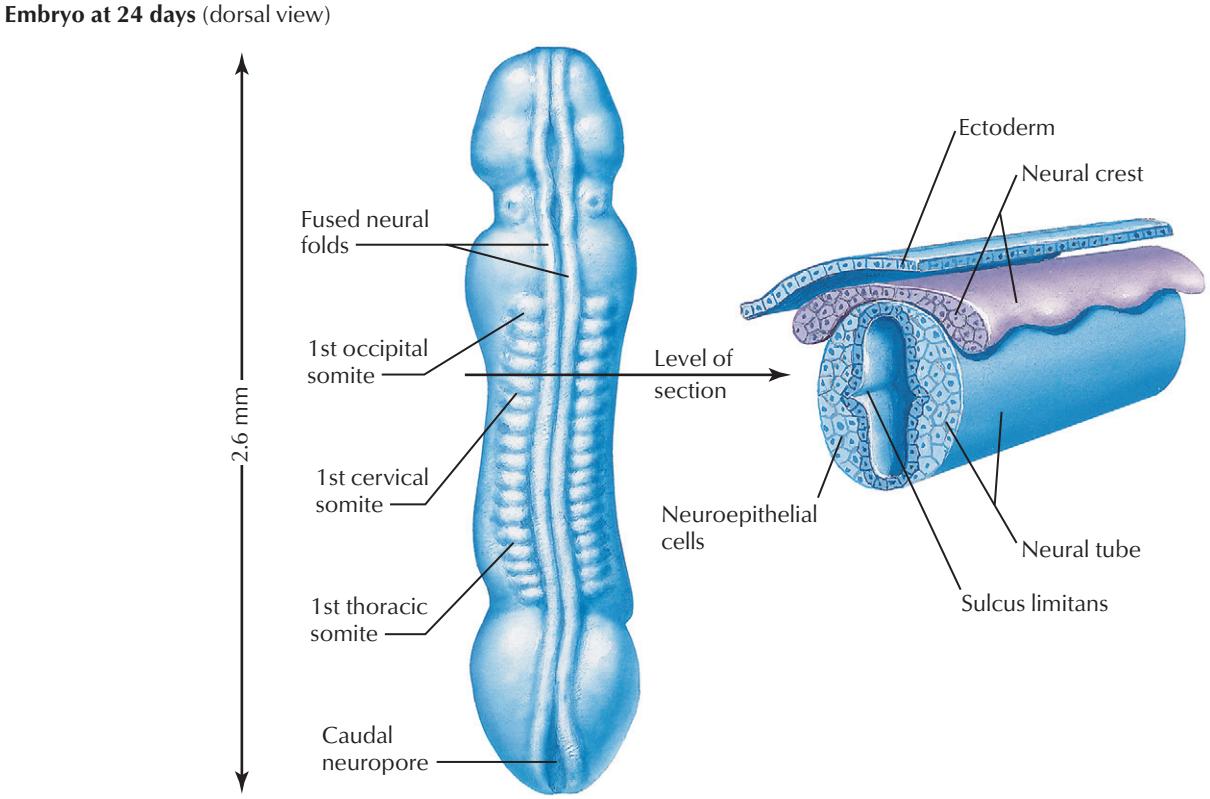


FIGURE 3.7 DEVELOPMENT OF THE CELLULAR SHEATH OF AXONS

Oligodendrocytes are equivalent to Schwann cells in the central nervous system. Axon sheaths are either **myelinated** or **unmyelinated.** Myelinated sheaths are designed for fast nerve conduction (e.g., in somatic nerves). The supporting cell wraps its membrane around the neuron process, and myelination results from the higher contribution of cell membrane relative to cytoplasm in the sheath. Unmyelinated sheaths (e.g., in slow-conducting autonomic neurons) are enveloped by supporting cells, but not in spiral fashion. In the myelinated axons of peripheral nerves, one Schwann cell will surround only one axon.



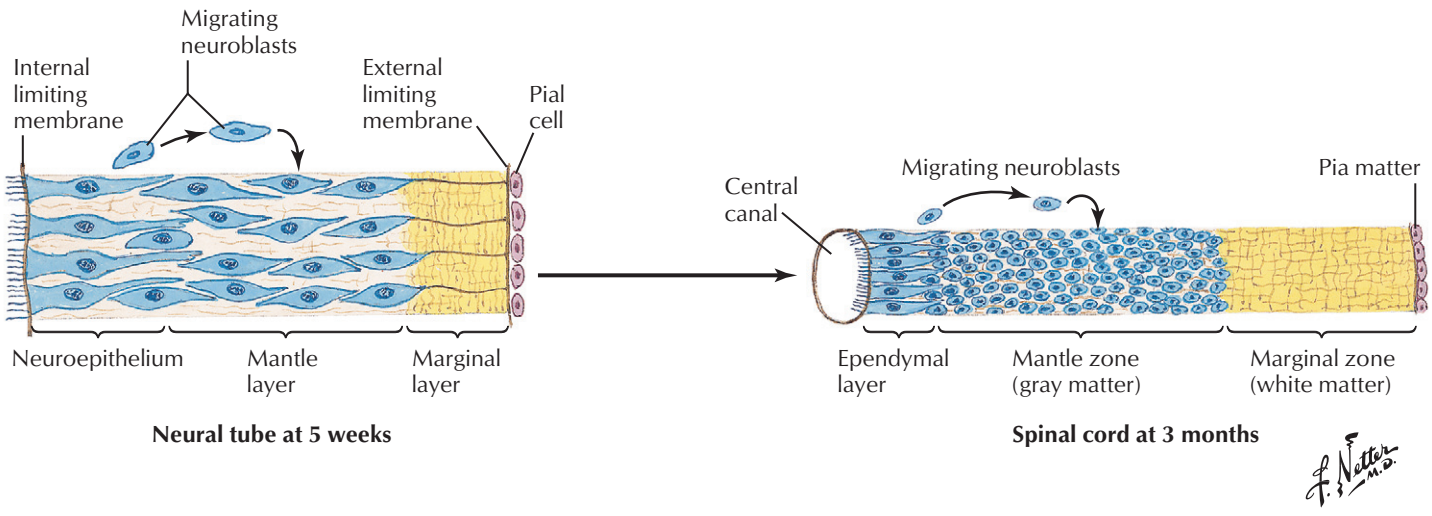
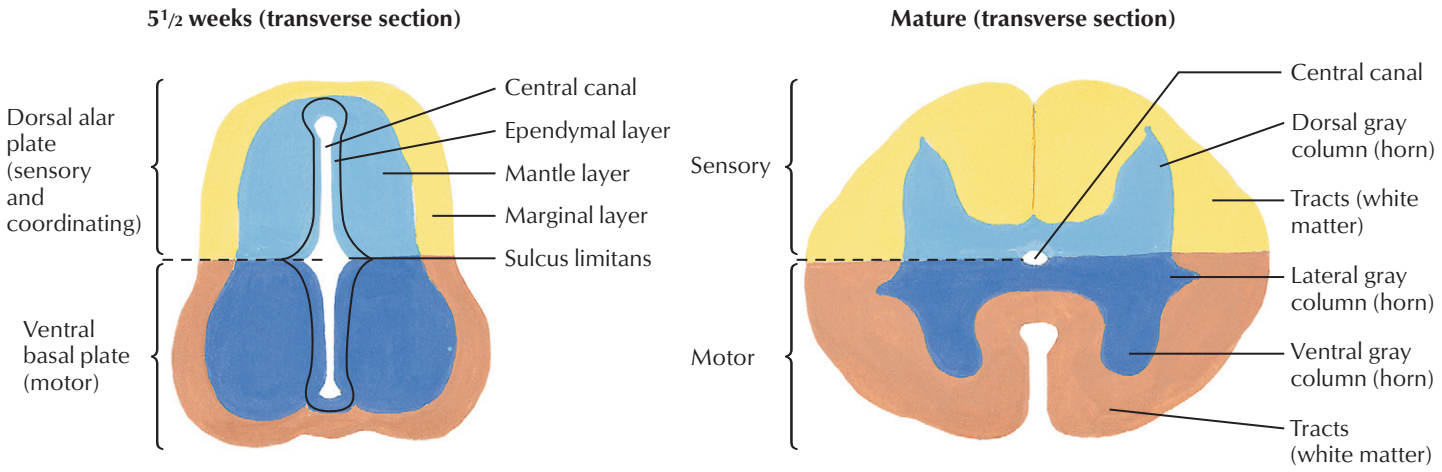


FIGURE 3.8 DEVELOPMENT OF THE SPINAL CORD LAYERS

The neuroepithelium gives rise to three layers. The inner **ependymal zone** will become the ependymal epithelium lining the diminishing central canal of the spinal cord. The **intermediate (mantle) zone** will develop into the gray matter of the spinal cord, the location of nerve cell bodies. The outer **marginal zone** will become white matter as neuron cell processes grow into it from the mantle layer. These axons will extend from the spinal cord to the brain as sensory tracts or descend from the brain to spinal cord levels as motor tracts. **Glial** cells and rich capillary networks are found in both the mantle and marginal zones.



Differentiation and growth of neurons at 26 days

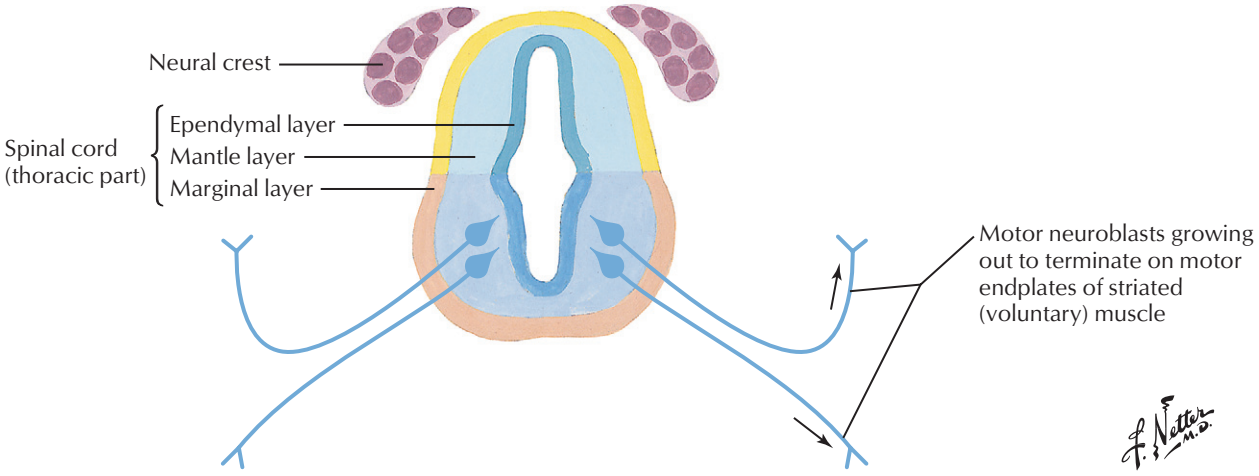


FIGURE 3.9 ALAR AND BASAL PLATES

The sulcus limitans is a longitudinal groove on each side of the central canal that divides the neural tube into a dorsal **alar plate** and ventral **basal plate.** The alar plate contains the cell bodies of neurons with sensory functions in the dorsal horn of gray matter. They receive input from sensory neurons in the spinal nerves. Somatic and autonomic motor neurons develop in the ventral and lateral horns of gray matter in the basal plate. Their axons leave the spinal cord as the ventral roots of spinal nerves. The neuron processes within the white matter are organized into tracts (funiculi) that relate to specific functions. Ascending sensory tracts and descending motor tracts do overlap with each other and do not segregate neatly into alar and basal plates.

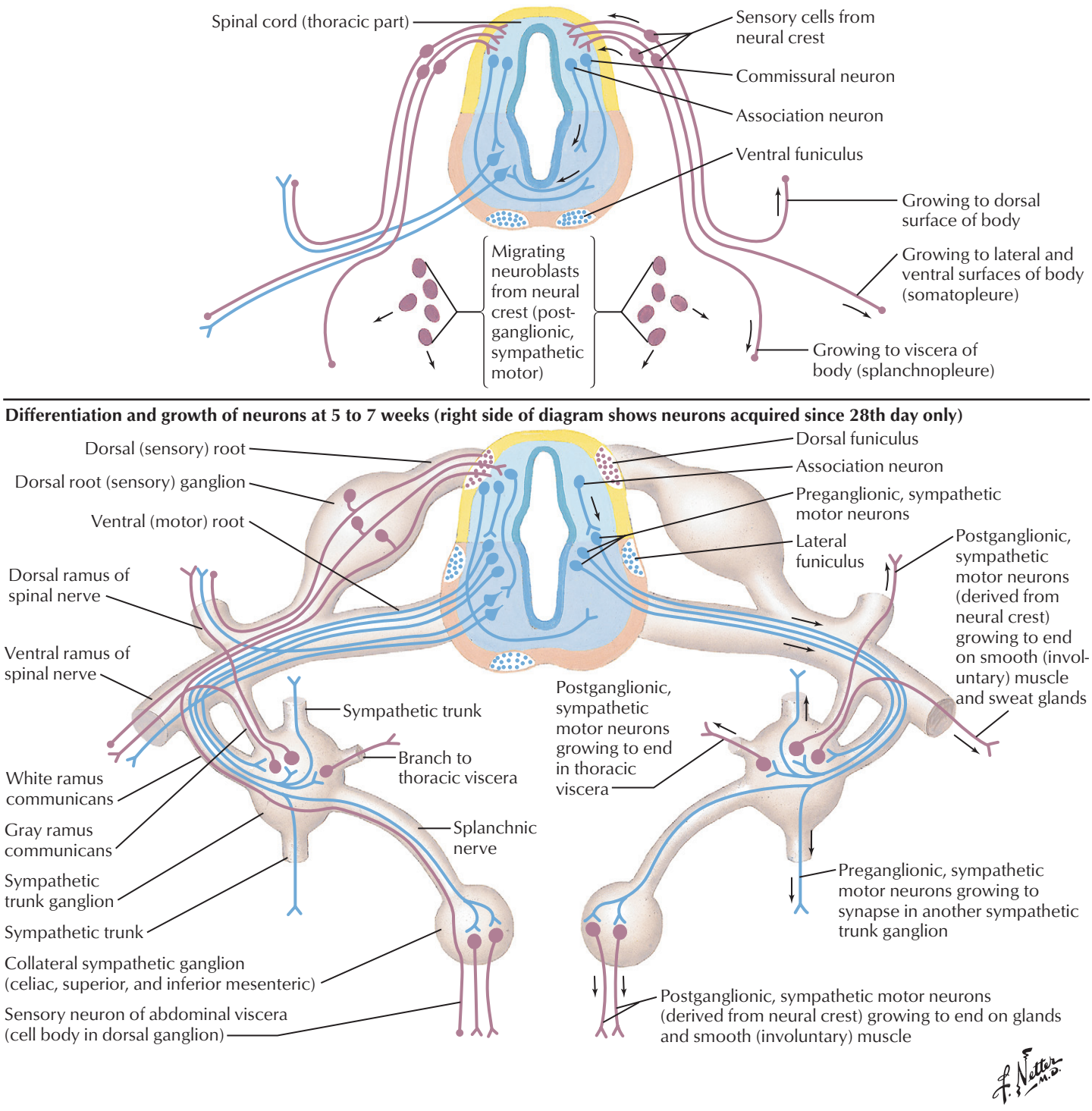
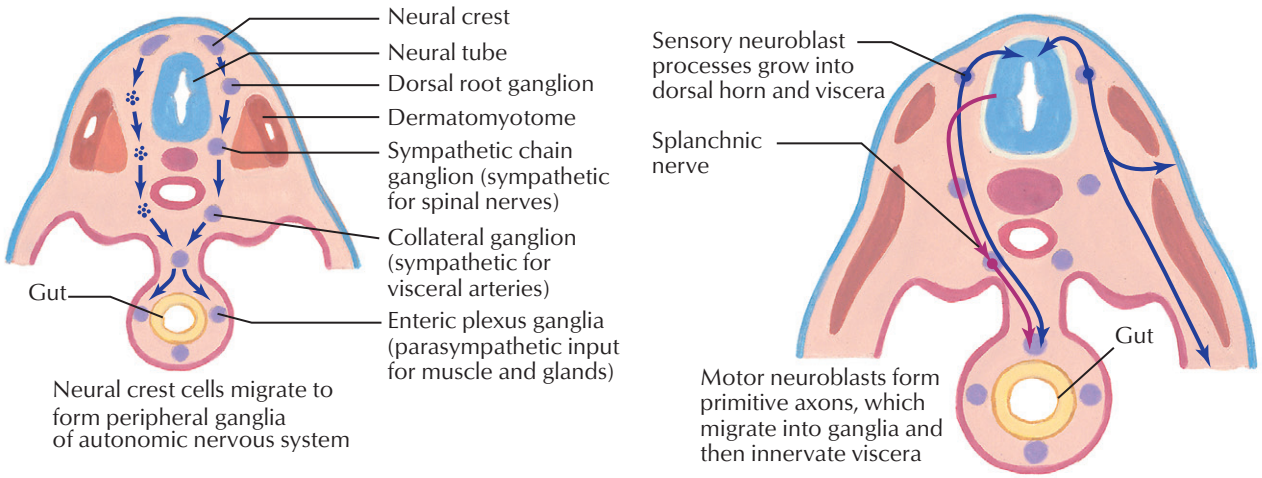


FIGURE 3.10 DEVELOPMENT OF THE PERIPHERAL NERVOUS SYSTEM

Dorsal sensory roots and ventral motor roots form the spinal nerves that innervate the body wall of bone, muscle, connective tissue and skin. At 28 days, the sensory and motor cell processes are growing into the dorsal and ventral aspects of the body wall via the **dorsal and ventral rami** of spinal nerves. Autonomic neuron processes leave the spinal nerves to go to the viscera via **splanchnic nerves** (or rejoin spinal nerves). Sympathetic neurons will synapse with a second neuron in the **sympathetic trunk** or **collateral (preaortic) ganglia.** Parasympathetic neurons (in the vagus and pelvic splanchnic nerves) will synapse in scattered ganglia within the walls of visceral organs.



Innervation of somatopleure (body wall) derivatives by the somatic nervous system *(spinal nerves)*.
On the left is the organization of motor innervation to the back *(blue neurons)* and limbs *(yellow and green neurons)*.
On the right is motor innervation to trunk muscles *(light blue)* and sensory innervation in cutaneous nerves *(dark blue)*.
Sensory nerve processes are found in all nerves to muscle in addition to cutaneous nerves.
Sympathetic fibers supplying arterial smooth muscle are also in every spinal nerve branch.

FIGURE 3.11 SOMATIC VERSUS SPLANCHNIC NERVES

The embryonic basis of the division of the peripheral nervous system into spinal (somatic) nerves and splanchnic autonomic nerves is the distinction between **somatopleure** and **splanchnopleure.** The former develops from ectoderm and the somatic part of lateral plate mesoderm. Somite hypoblasts migrate into it to form the lateral and ventral aspects of the body wall, including the limbs. Visceral organs develop from splanchnopleure derived from endoderm and lateral plate mesoderm. The ventral rami migrate into somatopleure; splanchnic nerves grow into splanchnopleure. Thoracic and lumbar splanchnic nerves have sympathetic and visceral sensory neurons. Pelvic spanchnic nerves (S2, S3, and S4) are parasympathetic and visceral sensory.

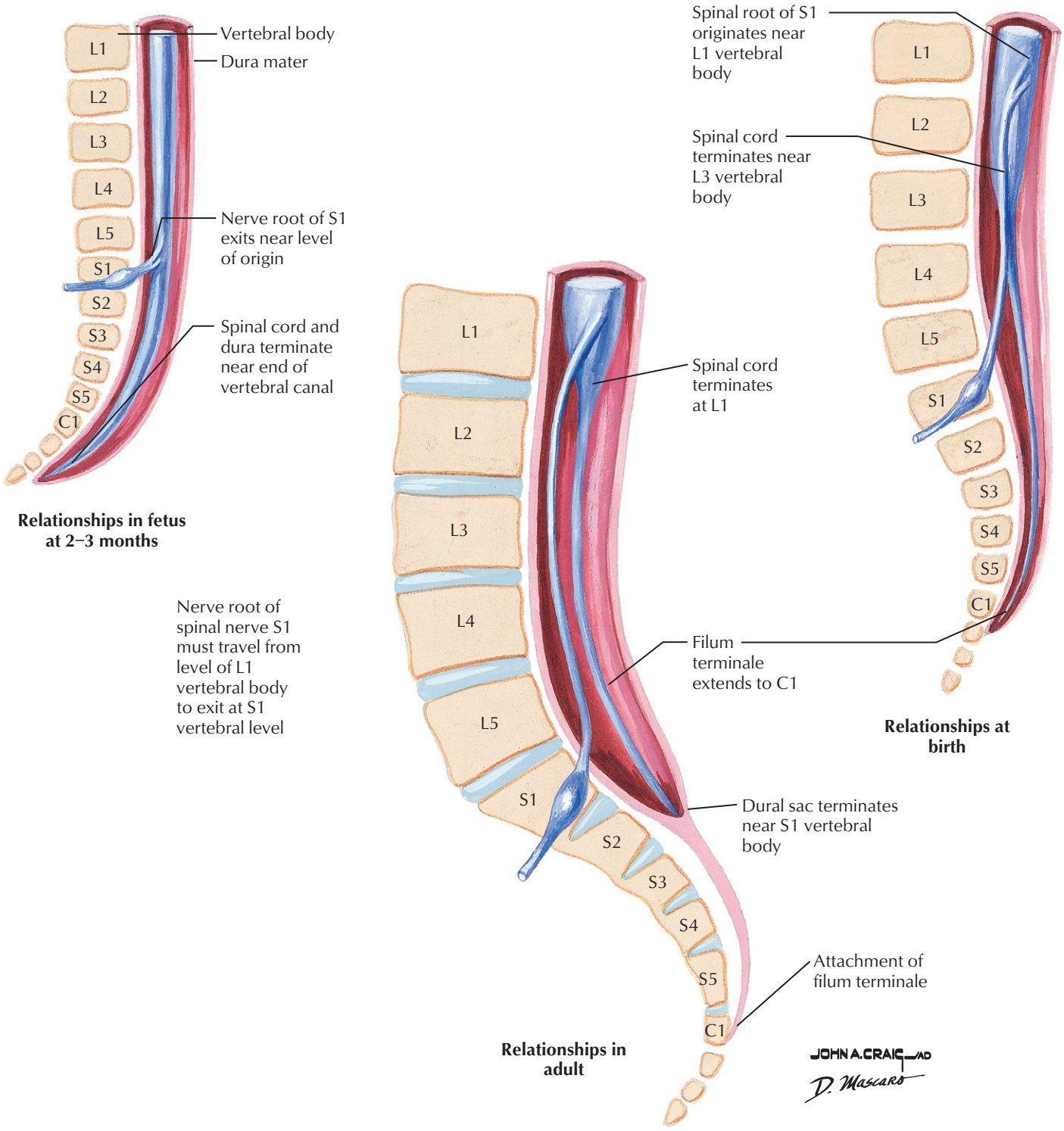


FIGURE 3.12 GROWTH OF THE SPINAL CORD AND VERTEBRAL COLUMN

The spinal cord and vertebral column are approximately the same length at the end of the embryonic period. The vertebral column grows at a relatively faster rate through the fetal and postnatal periods of growth until the lower end of the spinal cord is at the L1–L2 vertebral level in the adult. Lumbar and thoracic spinal nerve roots must pass inferiorly in the vertebral canal (as the **cauda equina,** or "horse's tail") to reach their appropriate level of exit from the vertebral column. The clinically significant result is that a needle can be passed into the subarachnoid space (to sample cerebrospinal fluid or inject anesthetic) below the level of L2 without danger of piercing the spinal cord. The subarachnoid space ends at upper sacral levels.

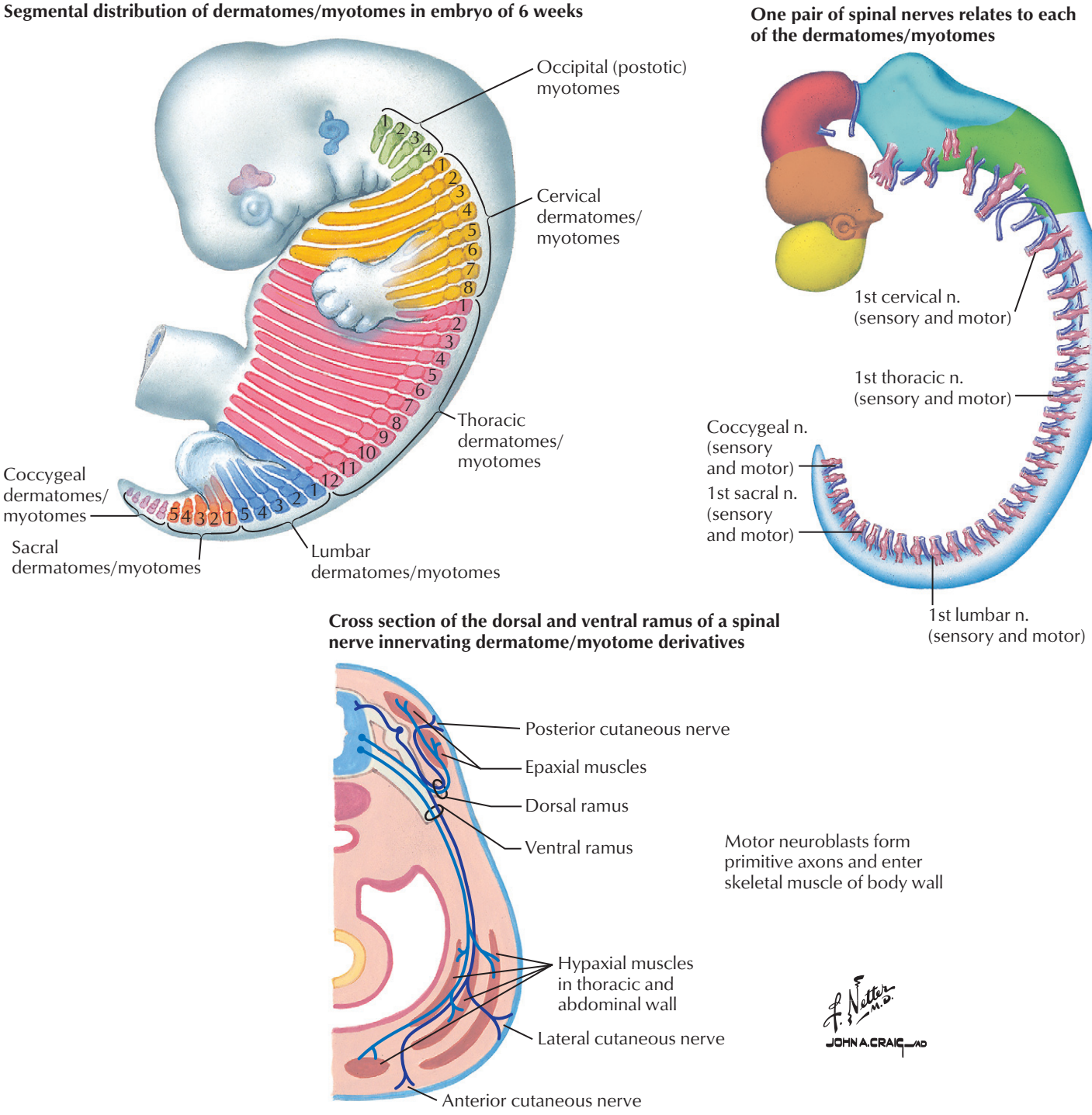
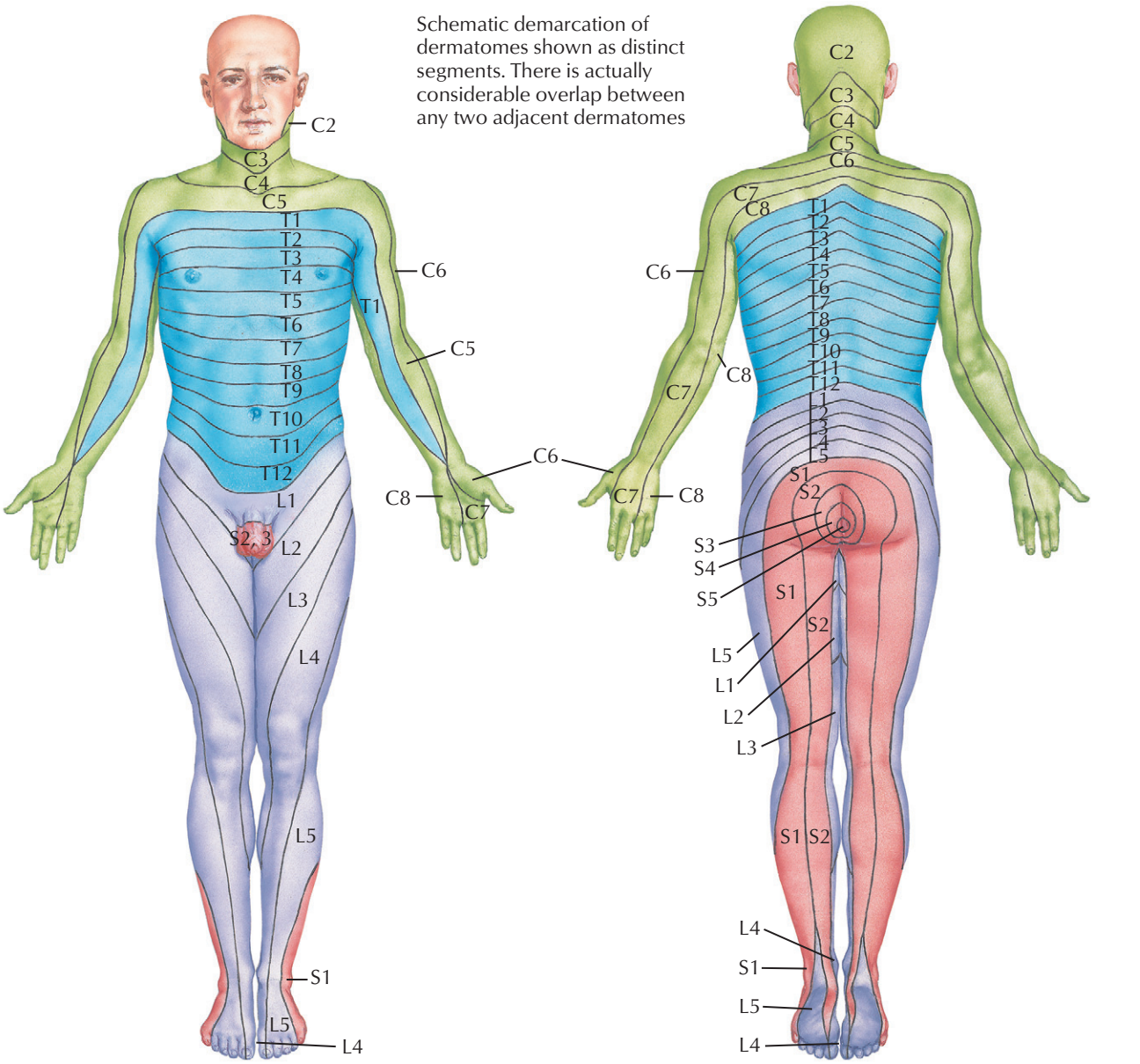


FIGURE 3.13 EMBRYONIC DERMATOMES

The somites from the paraxial columns of mesoderm in the embryo divide into a sclerotome, myotome, and dermatome. The sclerotome forms bone and cartilage, the myotome differentiates into muscle, and the dermatome contributes to the dermis of the skin. A single spinal nerve relates to each somite, and sensory neuron processes grow into the dermatome to supply its territory of skin via anterior, lateral, and posterior cutaneous nerves. Somatic mesenchyme from the lateral plate is also a source of the dermis and superficial fascia, particularly in the limbs, but the segmental pattern of skin innervation is established by the relationship between the spinal nerves and the dermatomes of the somites.



Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5, S1	Foot
L4	Medial side of great toe
S1, 2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum

F. Netter M.D.

FIGURE 3.14 ADULT DERMATOMES

A dermatome in the adult is defined as the area of skin supplied by a single pair of spinal nerves. As the limbs elongate and rotate, some dermatomes lose their continuity with the trunk, and the dermatomes of the lower extremity assume a spiral arrangement. Dermatomes in the limbs also differ from those in the trunk because spinal nerve segments are intermixed in the nerve plexuses that supply the extremities. As a result, one dermatome may be supplied by more than one nerve, and one nerve can contribute to more than one dermatome. Despite these complications, the craniocaudal relationship between dermatomes in the embryo is maintained in the adult. See Chapter 8 on the musculoskeletal system for more details on the effect of limb rotation on dermatomes.

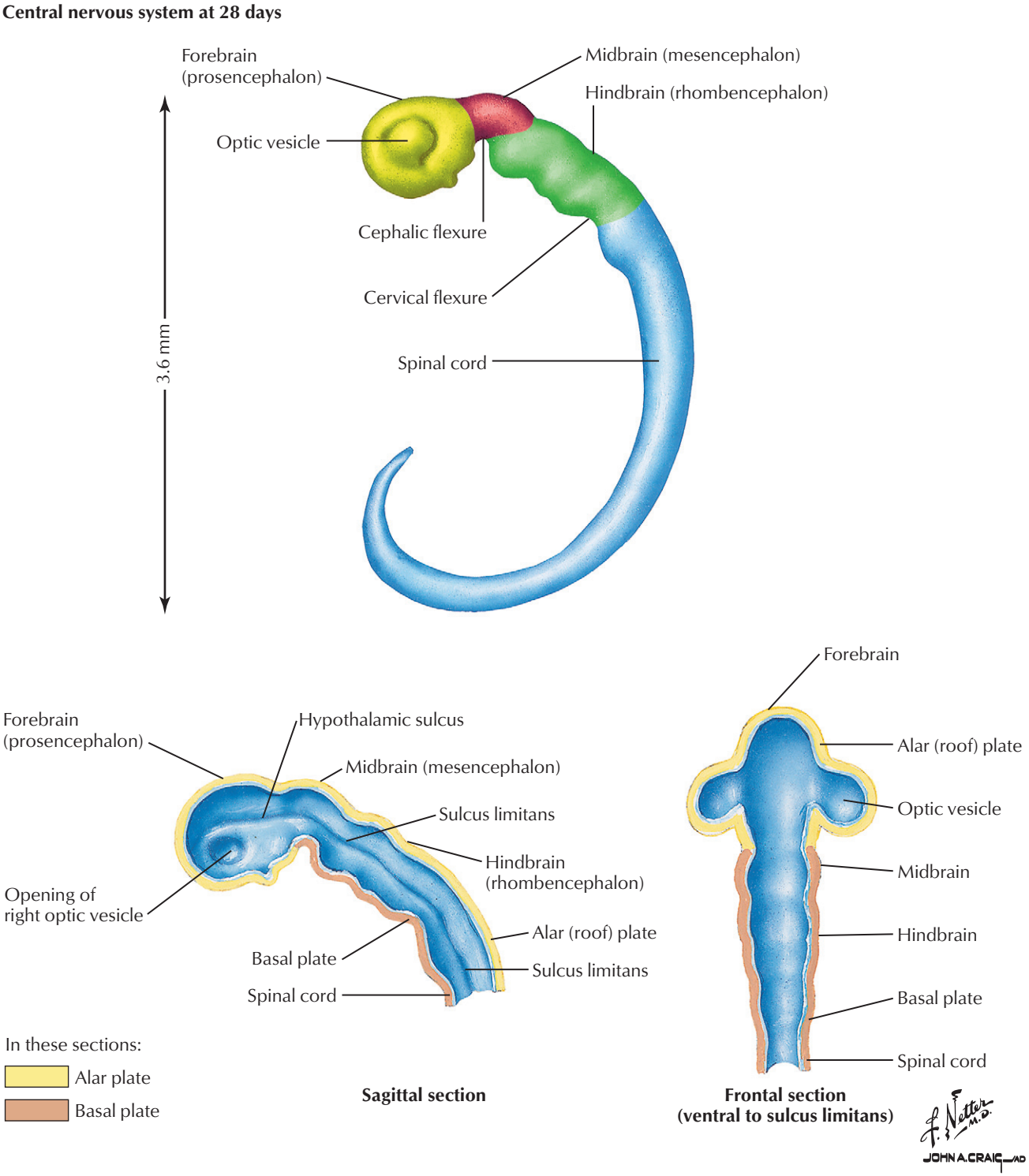


FIGURE 3.15 EARLY BRAIN DEVELOPMENT

The brain begins to develop from the neural tube near the end of the first month. Flexures and swellings distinguish the forebrain **(prosencephalon),** midbrain **(mesencephalon),** and hindbrain **(rhombencephalon).** Large **optic vesicles** extend from the forebrain and are the most prominent external features of the primitive brain. They will become the optic nerves and retina of the eyes. As in the spinal cord, the **sulcus limitans** divides the brain into a dorsal **alar plate** that is sensory and ventral **basal plate** that is motor. The exception is the forebrain, which has no basal plate. The only two cranial nerves that connect to the forebrain (olfactory and optic) are special sensory with no motor components.

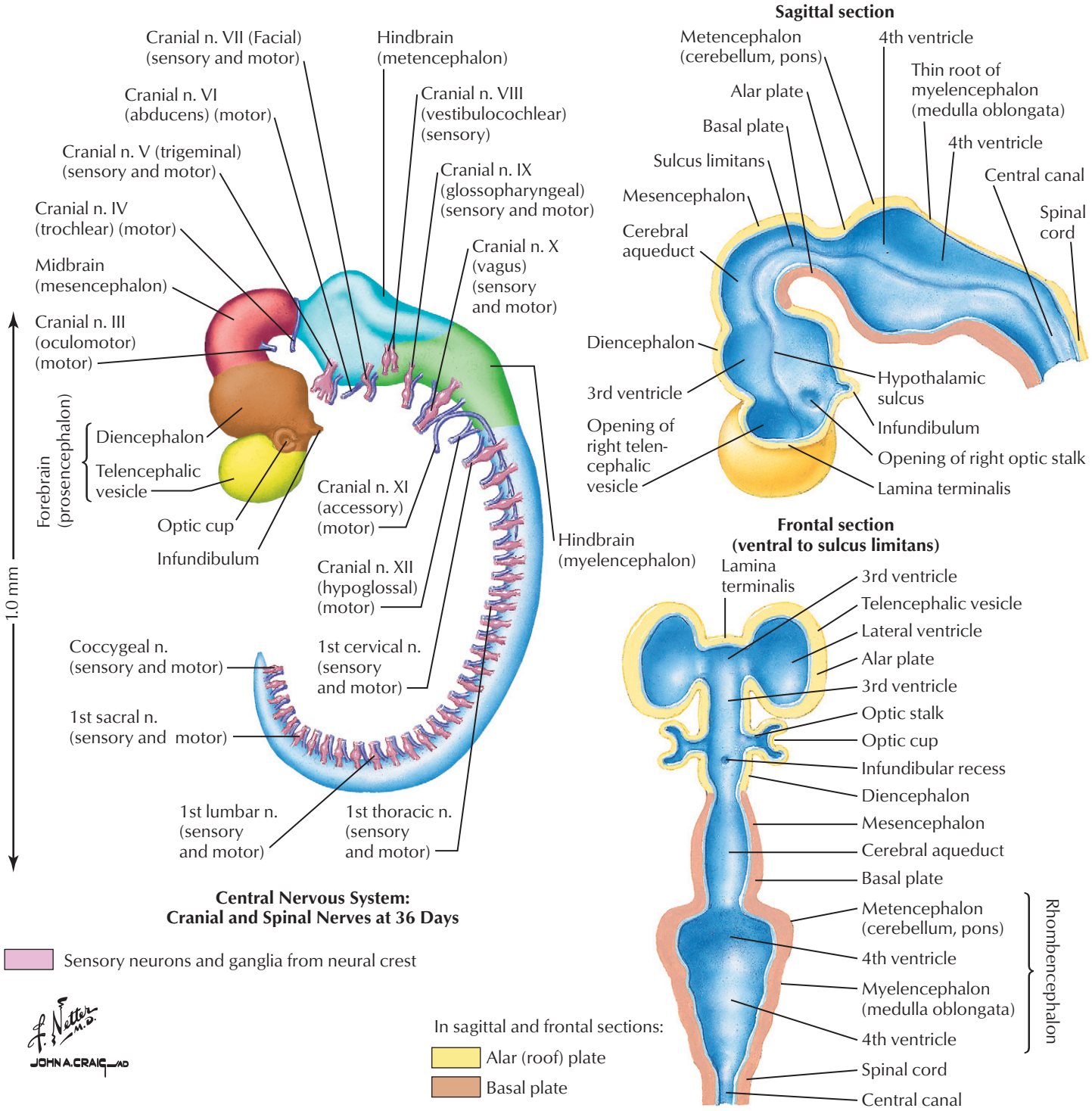


FIGURE 3.16 FURTHER DEVELOPMENT OF FOREBRAIN, MIDBRAIN, AND HINDBRAIN

By 5 weeks the forebrain has two subdivisions, the **telencephalon** and **diencephalon,** and the hindbrain has two parts, the **metencephalon** and **myelencephalon.** Each optic vesicle forms an **optic cup and stalk** extending from the diencephalon. The telencephalon is the future cerebral cortex. It consists of bilateral vesicles that grow rapidly to surpass the optic structures as the dominant features of the forebrain. The **infundibulum** (posterior lobe of the pituitary gland and connecting structures) extends from the floor of the diencephalon. The **hypothalamic sulcus** separates the thalamus from hypothalamus and is not a continuation of the sulcus limitans. The cavity of the neural tube develops into the ventricular system containing cerebrospinal fluid (see p. 78).

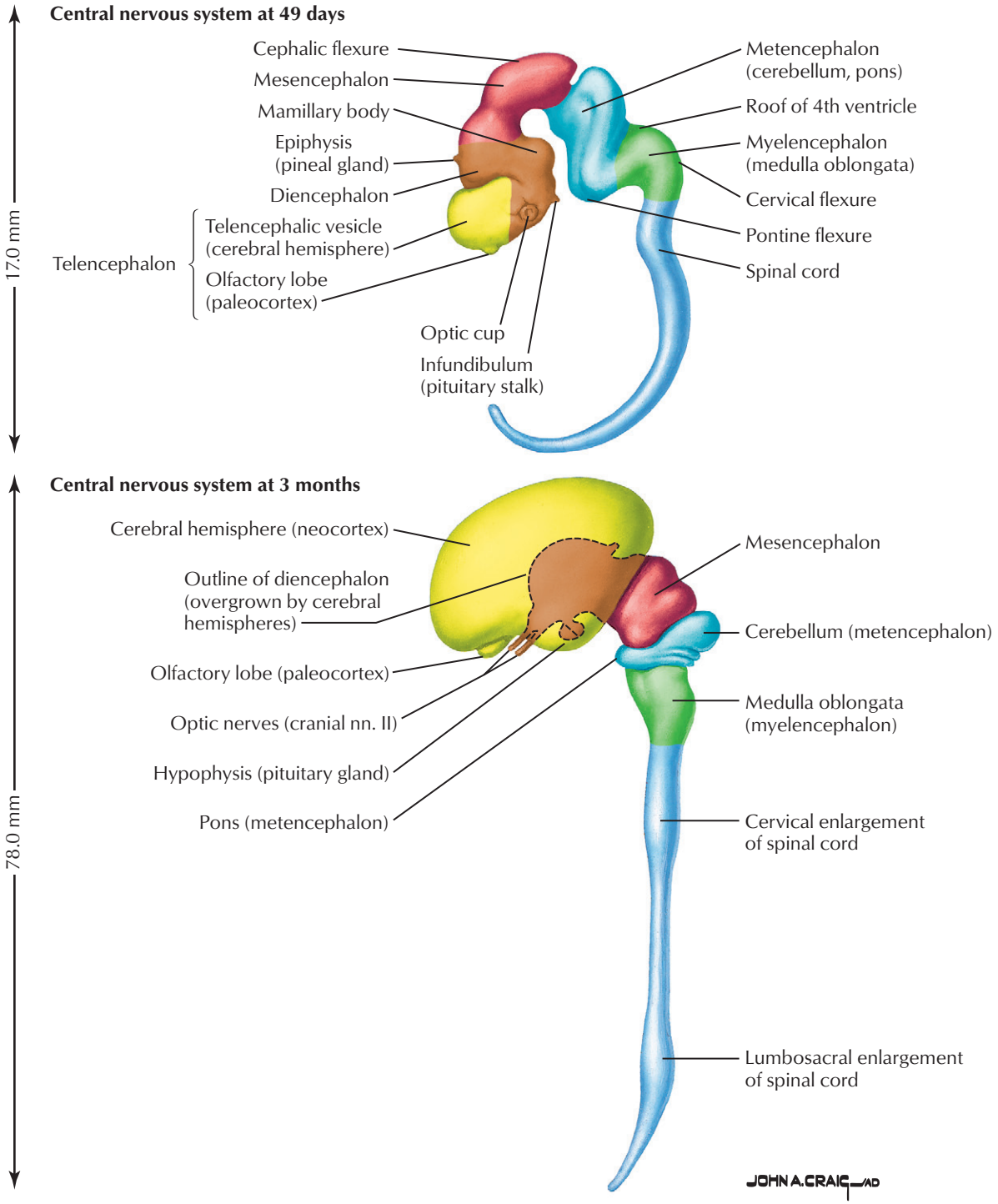


FIGURE 3.17 DEVELOPMENT OF MAJOR BRAIN STRUCTURES

By 3 months the major regions, structures, and features of the brain are recognizable. The **cerebral hemispheres** from the telencephalon overgrow the diencephalon. The **cerebellum** and **pons** differentiate from the metencephalon, and the myelencephalon is now the **medulla oblongata.** The **olfactory lobes** are prominent in the brains of lower animals, but in humans they become a restricted area of **"paleo"cortex,** and their proximal portions have evolved more complex structures of the **limbic system** (lobe) involved with emotions, memory, and learning. The cervical and lumbosacral enlargements of the spinal cord contain extra neurons required for the innervation of the limbs.

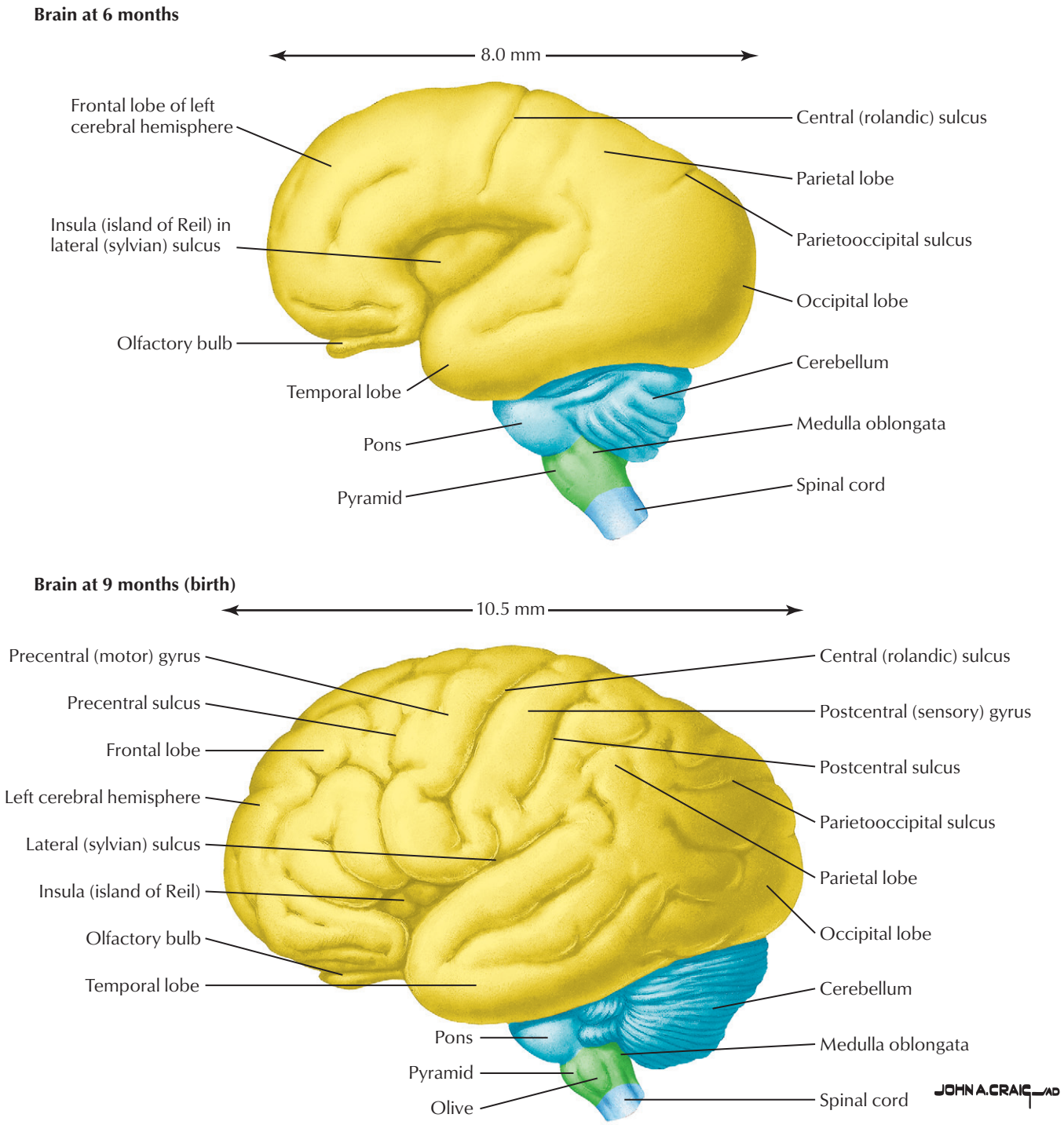
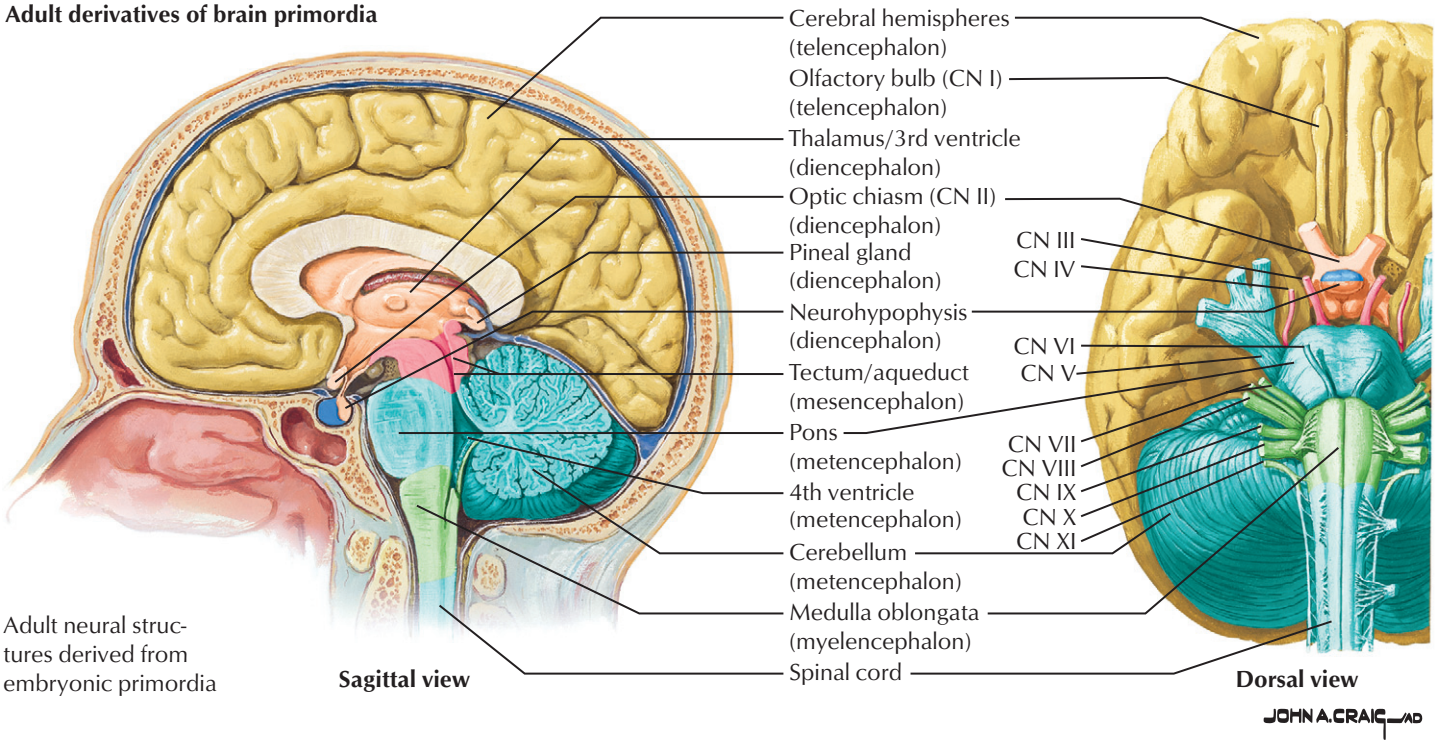


FIGURE 3.18 GROWTH OF THE CEREBRAL HEMISPHERES

The appearance of the brain changes dramatically from 3 months to birth with the rapid enlargement of the cerebral hemispheres and the elaboration of their **frontal, parietal, temporal,** and **occipital lobes.** The surface of the hemispheres becomes convoluted with primary, secondary, and tertiary **sulci** separating a number of irregular, folded **gyri.** This greatly increases the surface area of the cerebral cortex. Cortical enlargement is an evolutionary novelty related to higher mental function in mammals and birds, and most of this cortex is called **neocortex.** The human brain at birth is 25% of its adult weight (nearly 50% at 6 months, 75% at 2.5 years, 90% at 5 years, and 95% at 10 years).



ADULT DERIVATIVES OF THE FOREBRAIN, MIDBRAIN, AND HINDBRAIN

Forebrain	Telencephalon	Cerebral hemispheres (neocortex) Olfactory cortex (paleocortex) Hippocampus (archicortex) Basal ganglia/corpus striatum Lateral and 3rd ventricles	Nerves: Olfactory (I)
	Diencephalon	Optic cup/nerves Thalamus Hypothalamus Mammillary bodies Part of 3rd ventricle	Optic (II)
Midbrain	Mesencephalon	Tectum (superior, inferior colliculi) Cerebral aqueduct Red nucleus Substantia nigra Crus cerebri	Oculomotor (III) Trochlear (IV)
Hindbrain	Metencephalon	Pons Cerebellum	Trigeminal (V) Abducens(VI) Facial (VII) Vestibulocochlear (VIII) Glossopharyngeal (IX) Vagus (X) Hypoglossal (XII)
	Myelencephalon	Medulla oblongata	

FIGURE 3.19 DERIVATIVES OF THE FOREBRAIN, MIDBRAIN, AND HINDBRAIN

The telencephalon has three major components: the large **cerebral hemispheres, olfactory cortex** (including the hippocampus and limbic system), and **basal ganglia.** The latter two are intimately connected to the thalamus, epithalamus, and hypothalamus of the diencephalon for a number of integrative, autonomic, and endocrine control functions relating to a variety of mental processes. The midbrain **tectum** has visual and auditory integrative functions, and the ventral part has motor interconnections. The relatively large **cerebellum** functions in equilibrium, locomotion, and posture. The **medulla oblongata** and **pons** are sensory and motor relays between the spinal cord and brain and between the cerebrum and cerebellum; they also contain the motor nuclei of cranial nerves.

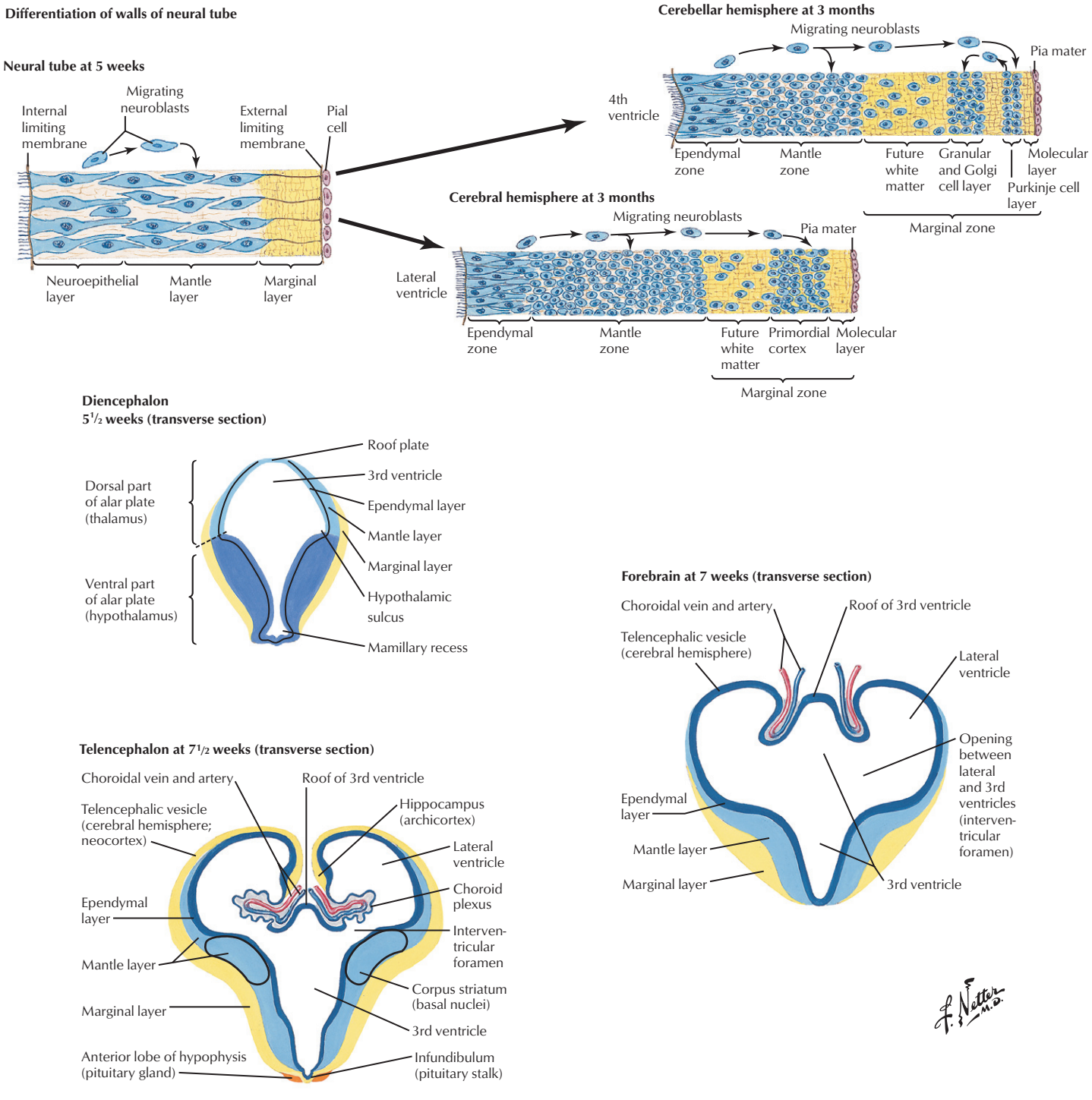


FIGURE 3.20 FOREBRAIN WALL AND VENTRICLES

Because of the evolutionary enlargement of the telencephalon of the forebrain, the cerebrum (neocortex) is the largest part of the brain and dominates its appearance in humans. It also differs from the organization of the central nervous system in the histological composition of the marginal zone and in the absence of the basal plate, the ventral, motor component of the neural tube.

Neuroblasts in the embryonic walls of the cerebral hemispheres (and cerebellum) migrate beyond the intermediate mantle zone to form gray matter layers in the outer marginal zone near the surface of the cortex. The cavity of the neural tube enlarges to form **lateral ventricles** in the cerebral hemispheres and **third ventricle** in the diencephalon.

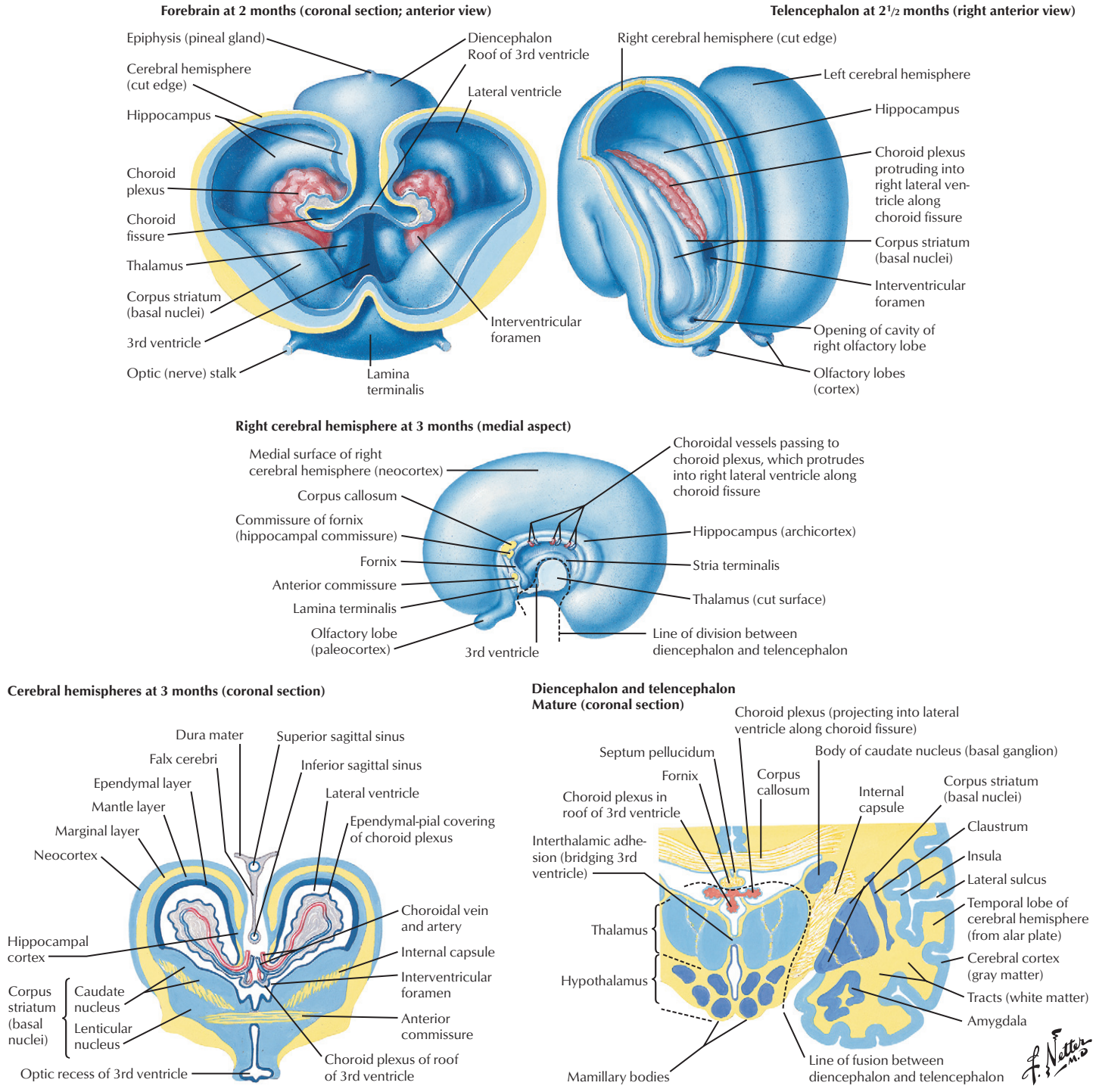


FIGURE 3.21 RELATIONSHIP BETWEEN TELENCEPHALON AND DIENCEPHALON

The diencephalon give rise to the epithalamus, thalamus, and hypothalamus. The epithalamus forms the pineal body and tela choroidea extending into the roof of the third ventricle. The telencephalon overgrows the diencephalon, and the basal ganglia and internal capsule of the telencephalon flank the thalamus and hypothalamus. The internal capsule is white matter connecting the cerebral cortex to the brainstem. Anterior to the diencephalon is the limbic system. Limbus is Latin for "border"; this proximal part of the olfactory cortex is at the structural and functional interface between telencephalon and diencephalon. The choroid plexus protrudes into the lateral ventricles to become the most extensive source of cerebrospinal fluid.

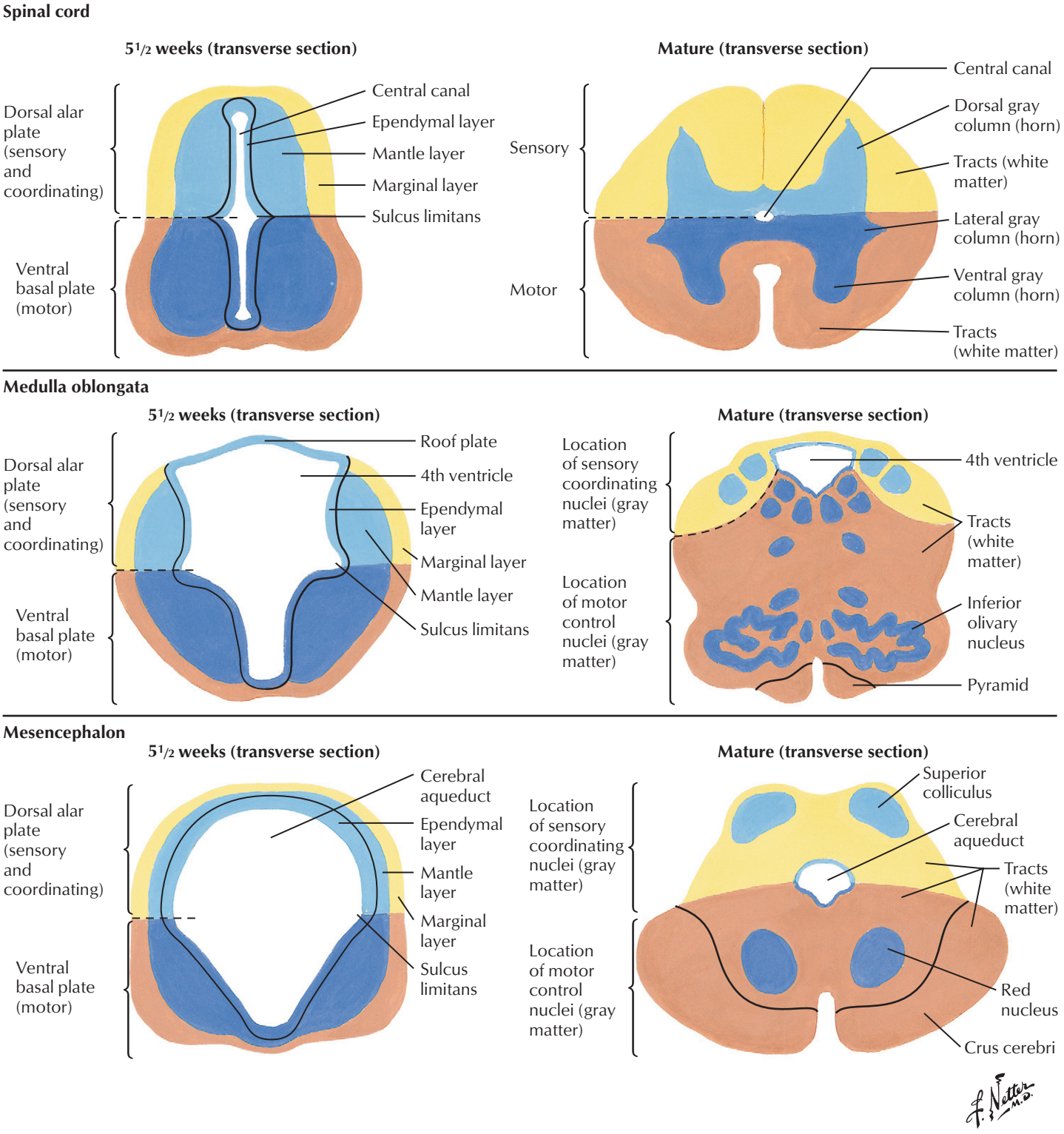


FIGURE 3.22 CROSS SECTIONS OF THE MIDBRAIN AND HINDBRAIN

The brain/brainstem and spinal cord have more similarities than may be apparent by casual inspection. Dorsal is sensory; ventral is motor. The sensory and motor gray matter columns of the spinal cord extend into the brainstem. Cranial and spinal nerves provide sensory and motor innervation to the body tissues in segmental fashion. These similarities are obscured by the loss of dorsal/ventral symmetry in the brain. Sensory areas are displaced laterally by the dorsal location of the ventricles. Other differences include the organization of brainstem gray matter into nuclei instead of columns and the greater variety of nuclei for new types of neurons in cranial nerves.

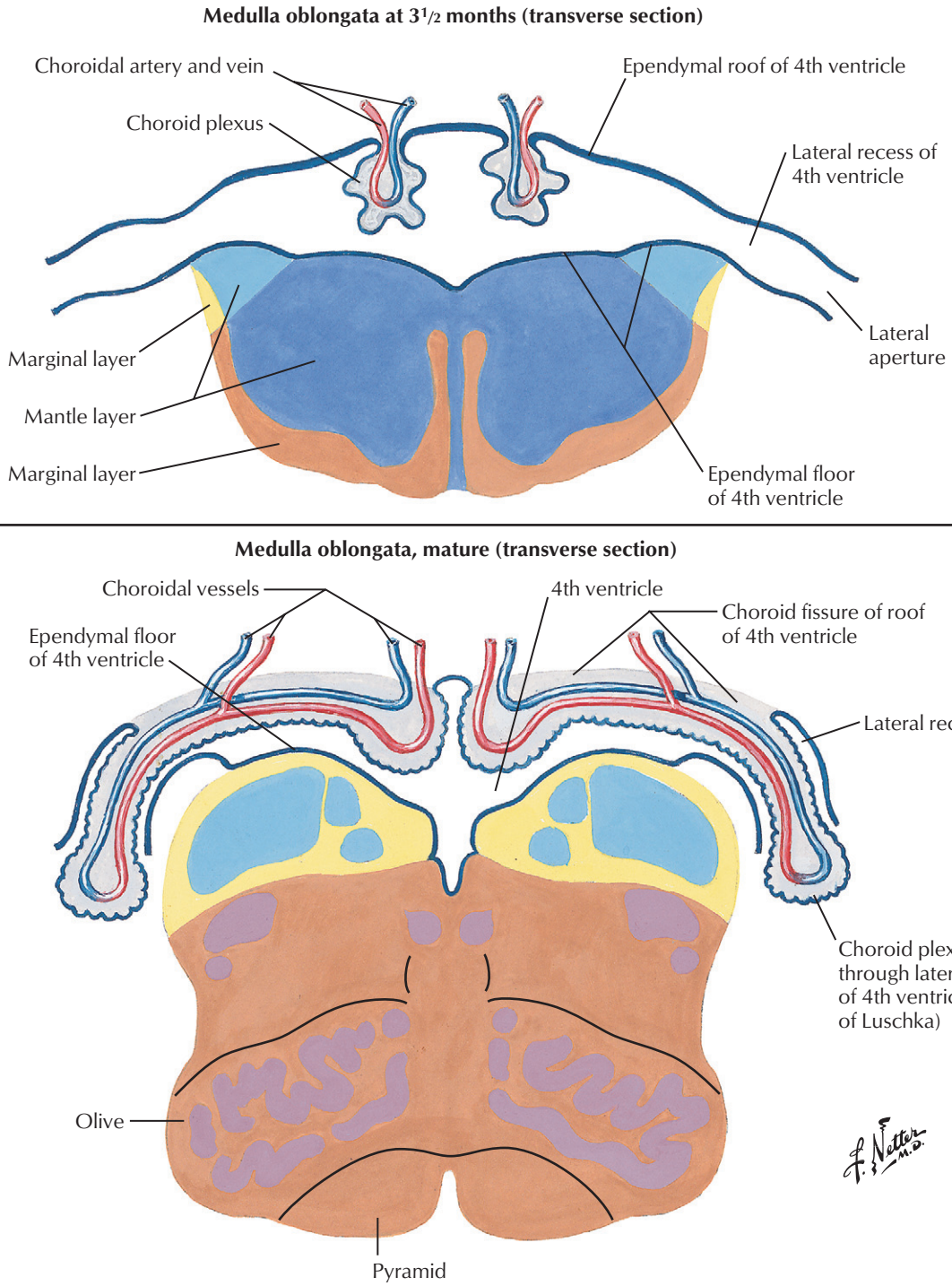


FIGURE 3.23 PRODUCTION OF CEREBROSPINAL FLUID

The ependyma, pia mater, and a rich plexus of blood vessels extend into the ventricles within the brain. This elaborate vascular membrane is the **tela choroidea** with its **choroid plexus** of capillaries, the site of production of **cerebrospinal fluid** (CSF) that surrounds and protects the brain and spinal cord in the subarachnoid space. CSF is an ultrafiltrate of arterial blood, and the tight junctions between the epithelial cells of the ependyma form a selective barrier in the passage of CSF from the choroid capillaries into the ventricles. Shown here schematically is the development of the choroid plexus in the roof of the **4th ventricle** in the medulla oblongata. The **foramina of Luschka** in the 4th ventricle are sites of passage of CSF into the subarachnoid space.

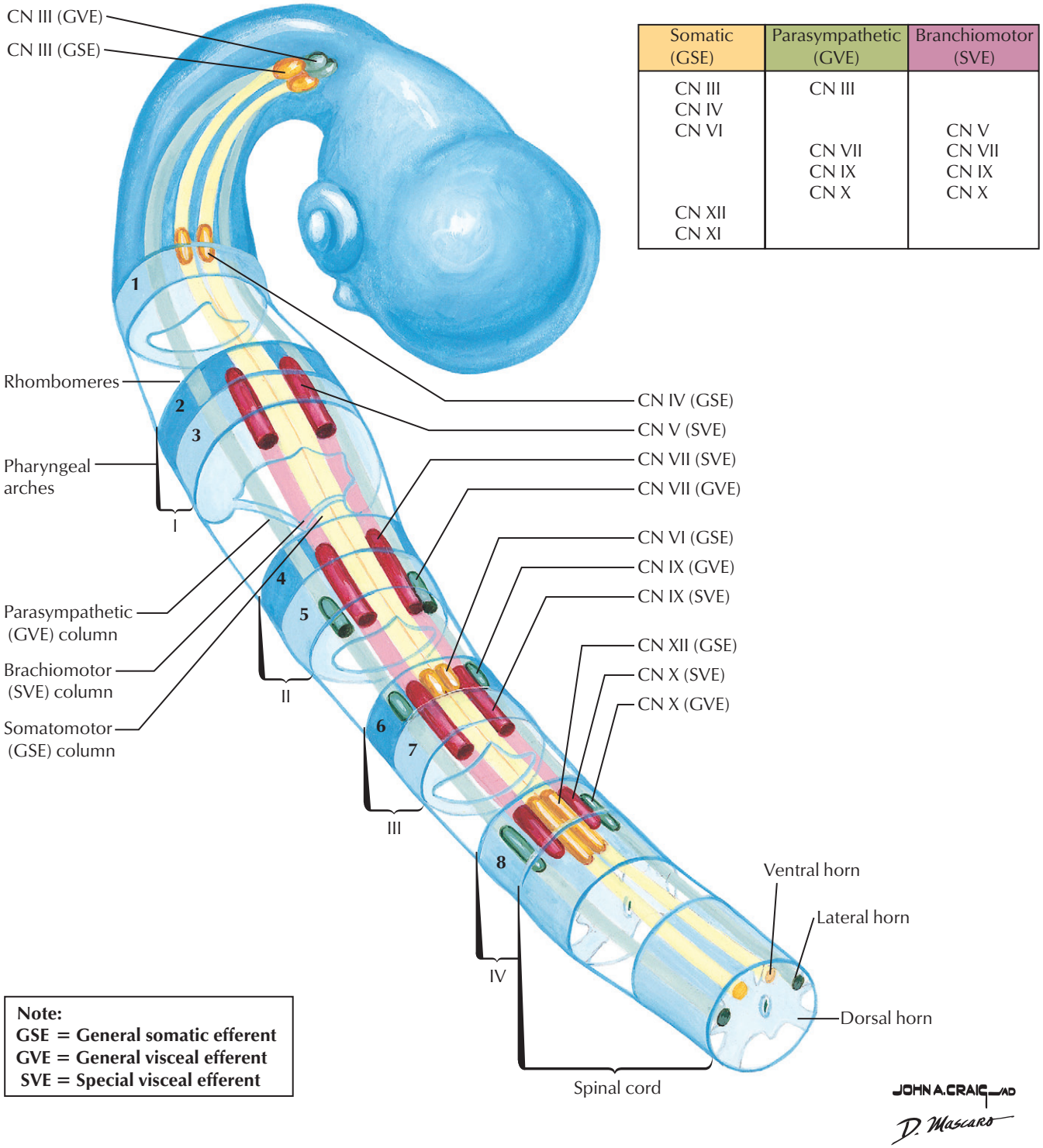


FIGURE 3.24 DEVELOPMENT OF MOTOR NUCLEI IN THE BRAINSTEM

The gray matter columns for somatomotor cell bodies (ventral horn) and presynaptic autonomic neurons (lateral horn) in the spinal cord extend into the brainstem. They maintain their same positional relationship to each other but are organized into a series of separate but aligned nuclei. A third series of nuclei is present in the hindbrain for motor neurons (branchiomotor) supplying the pharyngeal arch muscles.

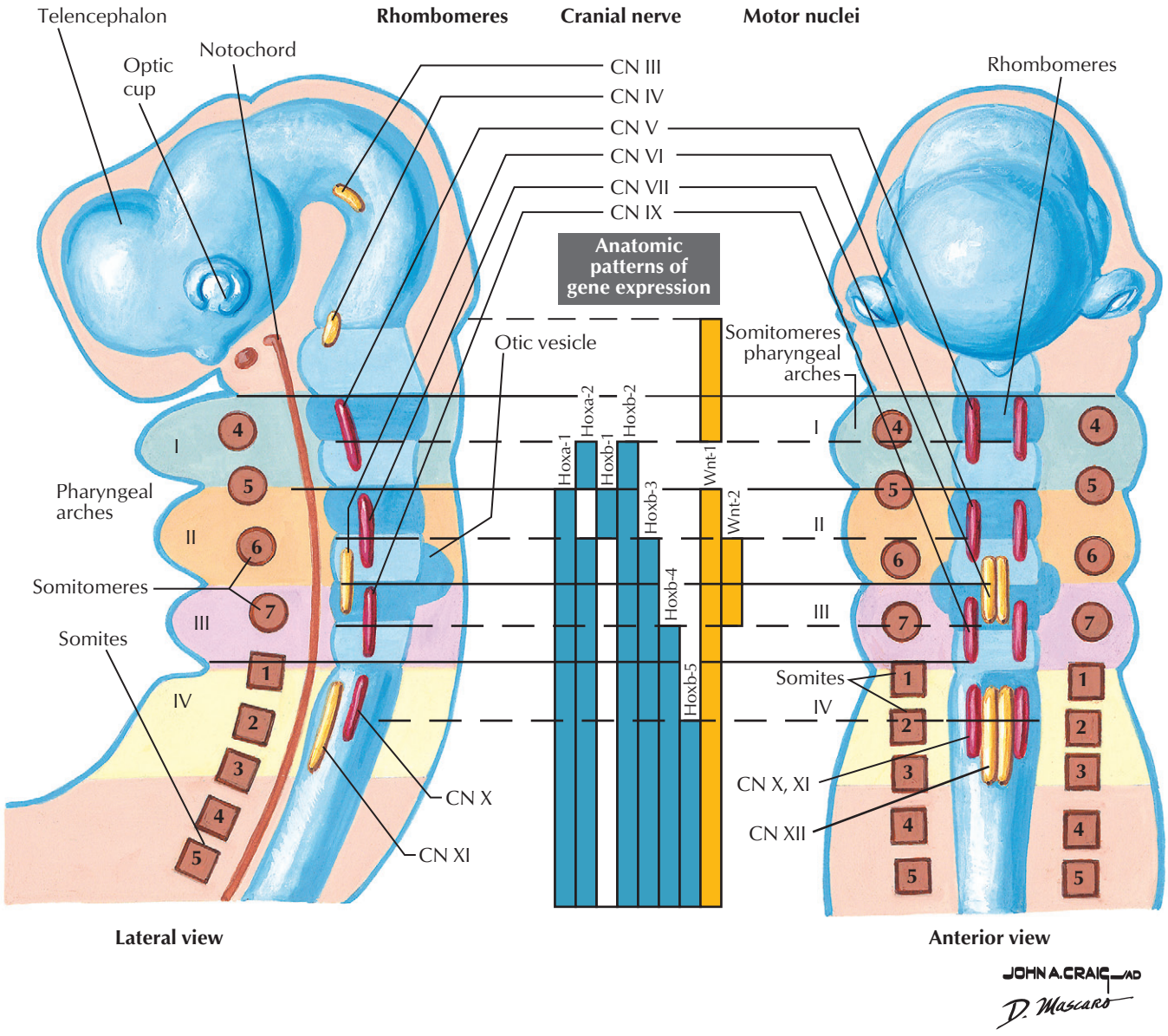
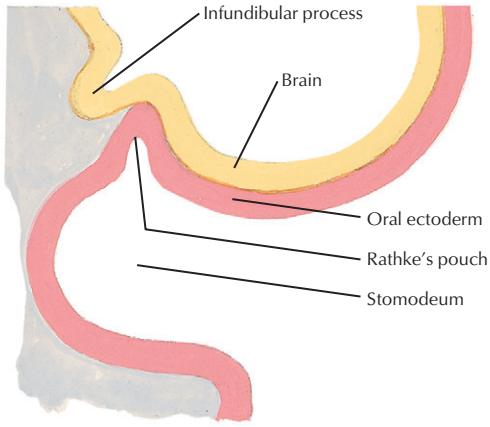
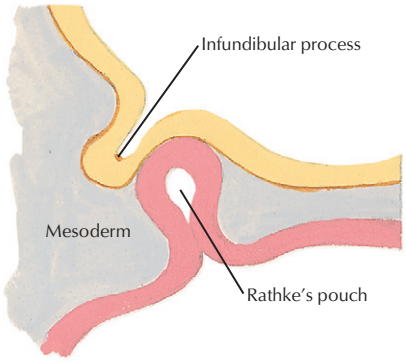


FIGURE 3.25 SEGMENTATION OF THE HINDBRAIN

Segmentation is evident in the hindbrain as a series of swellings and in the pattern of blood supply. This segmentation pattern is extended into the pharyngeal arches, somitomeres, and their nerves, which are all in register with the rhombomeres. Segmentation in these structures is related to the pattern of homeotic and segmentation gene expression (mainly of the *Hox* gene family). The segmental nature of the spinal nerves is obvious, but the developing spinal cord has no visible equivalent of rhombomeres, and the process that determines the path of peripheral neuron growth appears to be different in the hindbrain compared with that in the spinal cord.

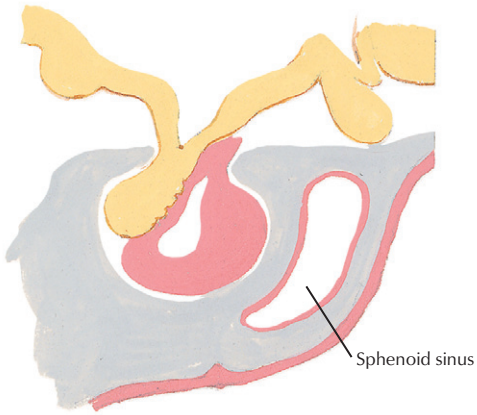


1. Beginning formation of Rathke's pouch and infundibular process

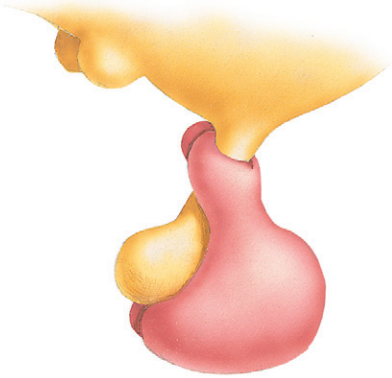


2. Neck of Rathke's pouch constricted by growth of mesoderm

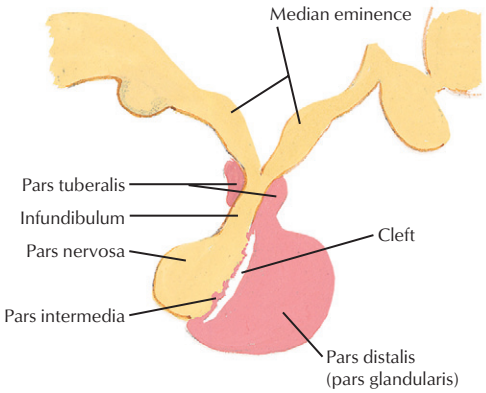
3. Rathke's pouch "pinched off"



4. "Pinched off" segment conforms to neural process, forming pars distalis, pars intermedia and pars tuberalis



5. Pars tuberalis encircles infundibular stalk (lateral surface view)



6. Mature form

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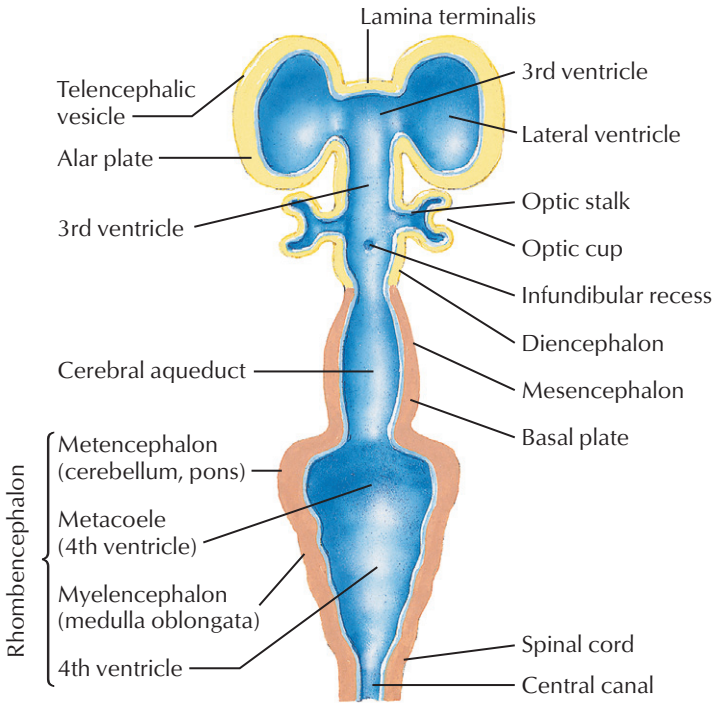
PITUITARY HORMONES

From the Anterior Lobe (Pars Distalis)		From the Posterior Lobe (Pars Nervosa)
Follicle-stimulating hormone (FSH)	Thyroid-stimulating hormone (TSH)	Vasopressin
Luteinizing hormone (LH)	Adrenocorticotropic hormone (ACTH)	Oxytocin
Prolactin	Growth hormone (GH)	

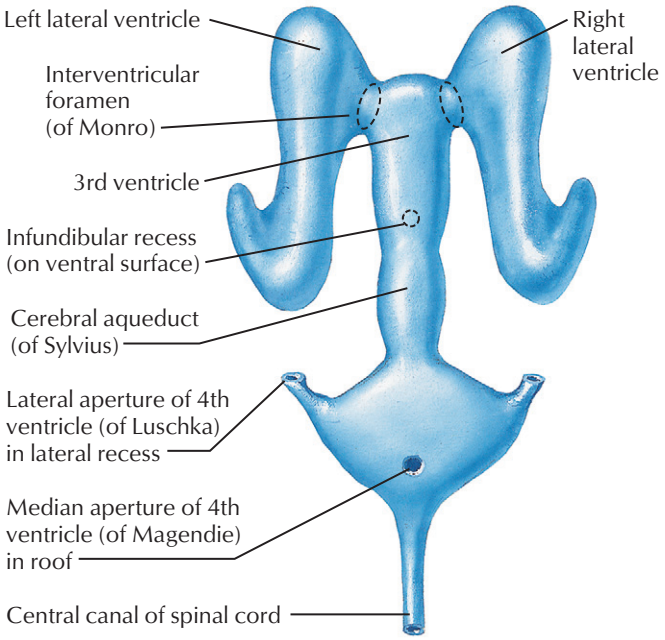
FIGURE 3.26 DEVELOPMENT OF THE PITUITARY GLAND

The pituitary gland is unusual in that it develops from the fusion of outgrowths from two embryonic primordia that are completely separate from each other in structure and function. The **anterior lobe** (**adenohypophysis** or **pars distalis**) is an outgrowth of the roof of the stomodeum. It encircles the base of the **posterior lobe** or **neurohypophysis,** which is an extension of the brain. The anterior lobe is glandular endocrine tissue that secretes its hormones in response to hypothalamic neuroendocrine products transmitted in the hypophyseal portal system of veins. The posterior lobe consists of specialized hypothalamic nerve terminations that store and release hormones.

Frontal section (ventral to sulcus limitans) at 36 days



Ependymal lining of cavities of brain at 3 months



Ependymal lining of cavities of brain at 9 months (birth)

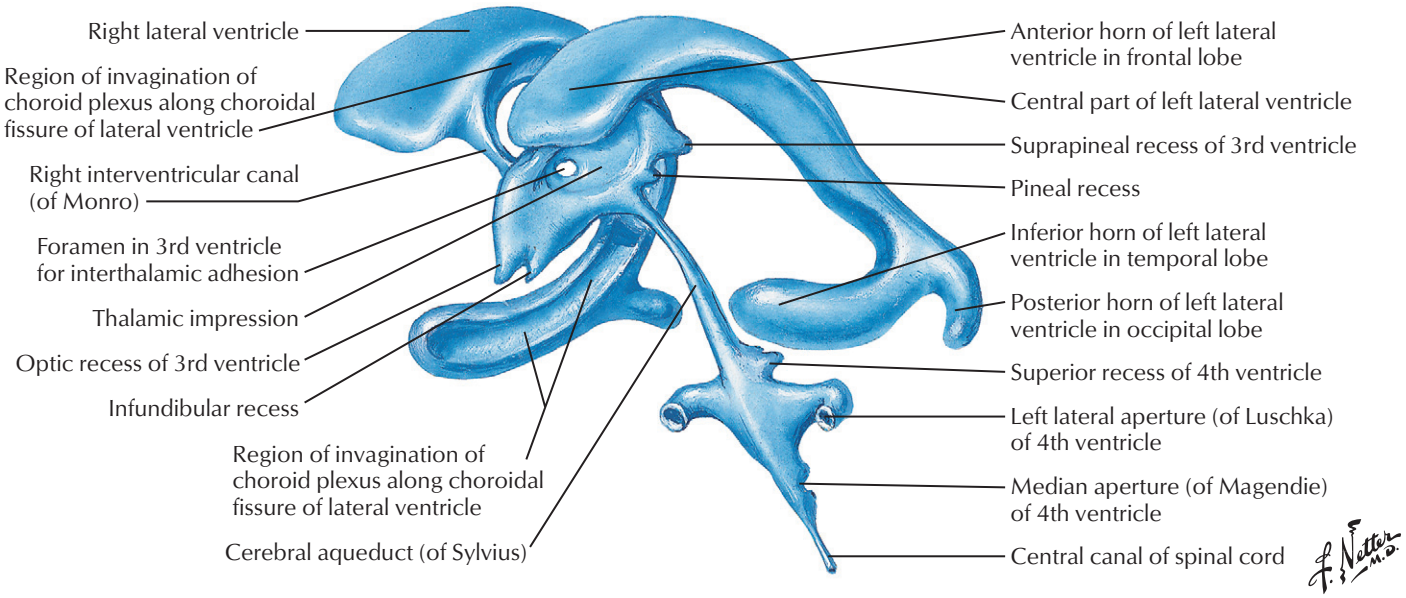


FIGURE 3.27 DEVELOPMENT OF THE VENTRICLES

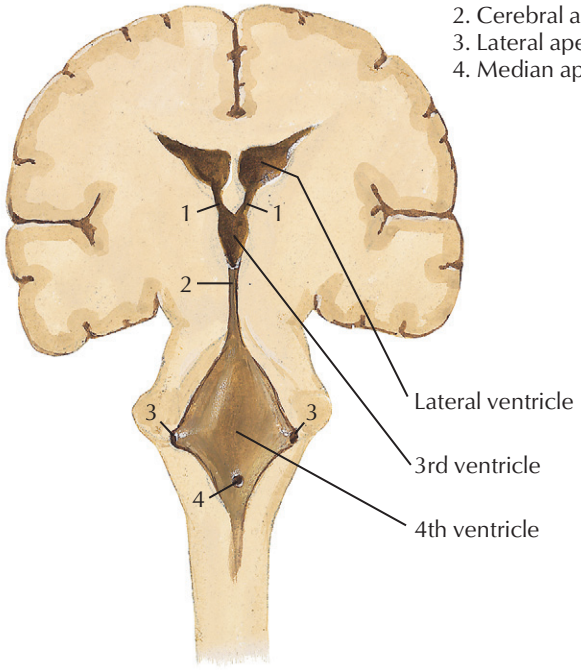
The lumen of the neural tube enlarges in the brain to form the **ventricles,** a series of interconnected chambers where **cerebrospinal fluid (CSF)** is produced. CSF exits the fourth ventricle from paired lateral apertures **(foramina of Luschka)** and a median aperture **(foramen of Magendie)** to surround the brain and spinal cord in the subarachnoid space. CSF reenters the bloodstream through arachnoid granulations that protrude into the superior sagittal sinus, a venous channel within the dura mater at the top of the falx cerebri, and through capillaries of the CNS and pia mater.

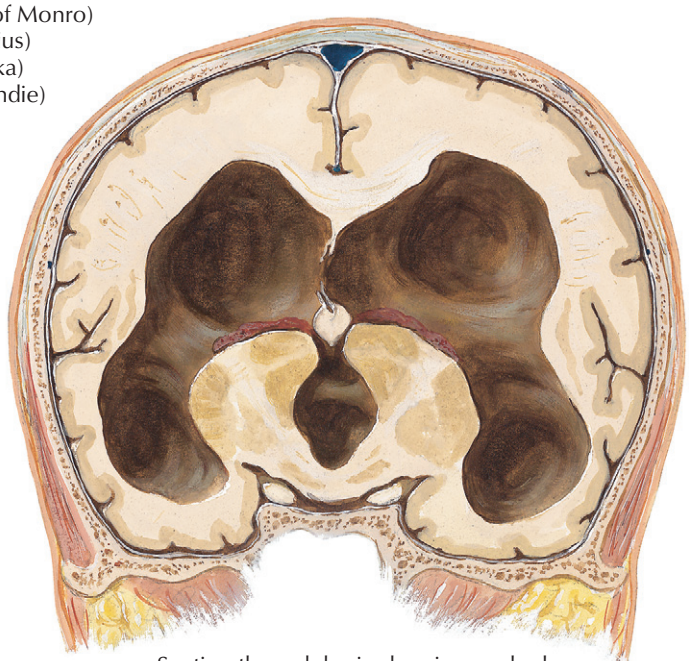
Hydrocephalus

Clinical appearance in advanced hydrocephalus

Potential lesion sites in obstructive hydrocephalus

1. Interventricular foramina (of Monro)
2. Cerebral aqueduct (of Sylvius)
3. Lateral apertures (of Luschka)
4. Median aperture (of Magendie)





Section through brain showing marked dilation of lateral and 3rd ventricles

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FIGURE 3.28 CONGENITAL VENTRICULAR DEFECTS

Obstructive hydrocephalus is a congenital type of "water in the head." Cerebrospinal fluid (CSF) accumulates within the ventricles due to a blockage of flow from one ventricle to another or from exiting the fourth ventricle into the subarachnoid space. The enlarging ventricles compress the brain against the neurocranium, which, in response to the increased pressure, grows at an abnormally fast rate compared with that of the viscerocranium. Postnatal hydrocephalus is more often caused by the interruption of CSF passing back into the bloodstream through the arachnoid granulations. Fluid accumulates in the subarachnoid space surrounding the brain instead of the ventricles, and the brain is compressed externally instead of internally.

Terminology

Auerbach's plexus	Part of the enteric nervous system, it is an autonomic plexus with ganglia in the smooth muscle wall of the gastrointestinal tract.
Central canal	Cavity within the neural tube. It diminishes within the spinal cord, but in the brain it forms the system of interconnected ventricles that produce cerebrospinal fluid.
Central nervous system	Brain and spinal cord.
Cortex	(L., "bark" or "shell") The outer, stratified, gray matter covering of the brain.
Dermatome	Area of skin innervated by one spinal nerve pair; or the part of a somite that gives rise to the dermis of skin supplied by one spinal nerve.
Enteric nervous system	Autonomic nerve plexus in the walls of the gastrointestinal tract.
Ganglion	(G., "swelling" or "knot") A collection of somatic (sensory) or autonomic nerve cell bodies in the peripheral nervous system.
Glia	(G., "glue") Supporting cells of the central nervous system, including astrocytes, oligodendrocytes, microglia, and ependymal cells.
Gray matter	Tissue in the central nervous system where cell bodies predominate in contrast to white matter consisting of nerve cell processes.
Meissner's plexus	Part of the enteric nervous system, it is an autonomic plexus with ganglia in the submucosa of the gastrointestinal tract wall.
Nerve	Collections of neuron cell processes enveloped by a connective tissue sheath of epineurium in the peripheral nervous system.
Nerve fiber	The long process of a single neuron enveloped by the connective tissue sheath of endoneurium.
Neural crest	Part of the folding neural tube that pinches off to form the cell bodies of all neurons and supporting cells outside the central nervous system. Also gives rise to pia, arachnoid, and mesenchyme in the head that will form bone, muscle, and connective tissue.
Neural plate	Thickening of ectoderm in the bilaminar embryonic disc that gives rise to all of the nervous system.
Neural tube	Tube derived from surface ectoderm that gives rise to the brain and spinal cord (central nervous system) and all of the nerve cell bodies within them.

Terminology, cont'd

Neurotransmitter	Chemical that relays an electrical impulse from one neuron to another at the synapse, the narrow gap between neurons. Also effects its action on muscle, glandular epithelium, and so forth at the end of a nerve.
Node of Ranvier	Gaps between Schwann cells along myelinated nerve fibers.
Nucleus	Discreet patch of gray matter in the brainstem where the cell bodies of neurons with specific functions are located.
Perineurium	Sheath around bundles of nerve cell processes in peripheral nerves that has epithelial, contractile, and connective tissue properties.
Peripheral nervous system	All cranial, spinal, and autonomic nerves that are in the body tissues outside the brain and spinal cord (central nervous system).
Plexus	(L., "braid") Interconnecting networks of peripheral nerves (or vessels).
Rhombomeres	Segmentation of the hindbrain related to the pattern of segmentation/homeotic gene expression (mainly *Hox* genes).
Somatopleure	Lateral plate mesoderm with surface ectoderm that is the basis for the body wall bone, striated muscle, skin, and connective tissue.
Somites	Epithelial blocks of mesoderm flanking the notochord that develop from the paraxial columns of mesoderm. They will form bone, muscle, and connective tissue.
Somitomeres	The first evidence of segmentation of the paraxial columns in the process of somite formation. In the head, they never fully separate into distinct somite blocks and retain the term, somitomeres.
Splanchnopleure	Lateral plate mesoderm with endoderm that forms the wall of visceral organs and their suspending mesenteries.
Sulcus limitans	Bilateral groove in the central canal dividing the neural tube into dorsal alar plates (sensory) and ventral basal plates (motor).
Tela choroidea	(G., "weblike membrane") Vascular layers of pia mater and ependyma in the walls of the ventricles that produce cerebrospinal fluid.
Tethered cord syndrome	A low positioning of the termination of the spinal cord below L1 by the filum terminale that may result from abnormal secondary neurulation. May be associated with sensory and motor symptoms in pelvic organs and the lower extremities.
White matter	Tissue in the central nervous system consisting largely of nerve cell processes extending from cell bodies in the gray matter.

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CHAPTER 4

THE CARDIOVASCULAR SYSTEM

HEART PRIMORDIUM

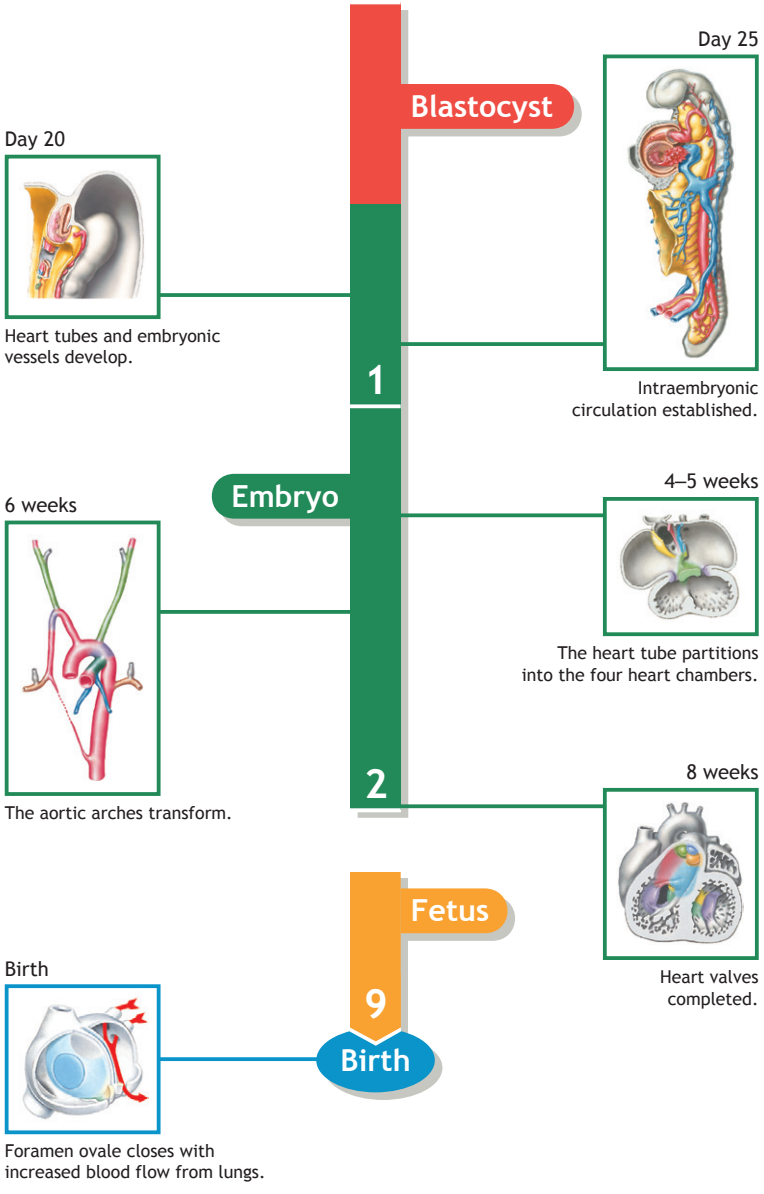
Cardiogenic mesoderm at the cranial end of the embryonic disc. Most is sphlanchnic mesoderm from the primitive streak. Mesoderm in the outflow portions of the heart is cranial mesoderm from the neural crest and paraxial columns.

PLAN

The cardiovascular system is the first functioning system. The heart begins as a primitive tube with peristaltic waves of contraction starting by day 22. Blood circulates within the embryo and to the placenta and yolk sac. The single heart tube is partitioned into four chambers, with a systemic outflow on the left and pulmonary outflow on the right. Pulmonary circulation is minimal because gas exchange occurs in the placenta and the airway is filled with amniotic fluid. Blood bypasses the nonfunctioning lungs in two temporary "shunts," one between the atria (foramen ovale) and one between the pulmonary trunk and aortic arch (ductus arteriosus). The fetal circulatory system is designed to be capable of converting to the adult pattern with the first breath.

TIMELINE

Prenatal Time Scale (Months)



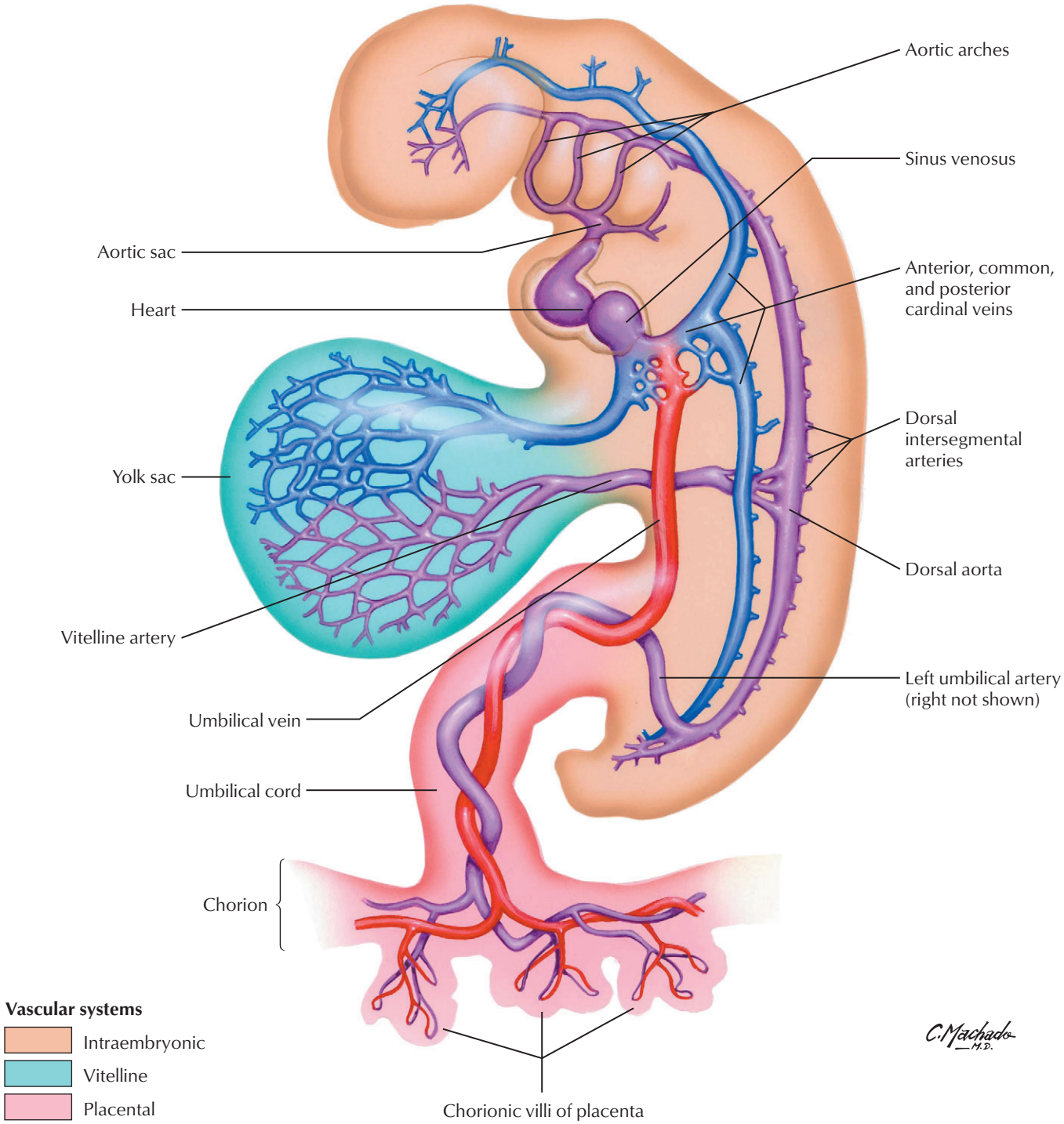


FIGURE 4.1 EARLY VASCULAR SYSTEMS

By the end of the third week, blood flow is established within the embryo and to the placenta and yolk sac. Oxygen and nutrients derived from maternal blood in the placenta enter the embryo in the umbilical vein. The primary intraembryonic arteries are the dorsal aorta, the intersegmental arteries between somites, and the aortic arch arteries within the pharyngeal arches in the head and neck region of the embryo. The cardinal system of veins brings embryonic venous blood back to the heart, where it mixes with blood from the umbilical vein. The yolk sac is not a primary source of nutrition as in egg-laying animals, but it is important as the first source of blood cells that enter the embryonic circulation via the vitelline veins.

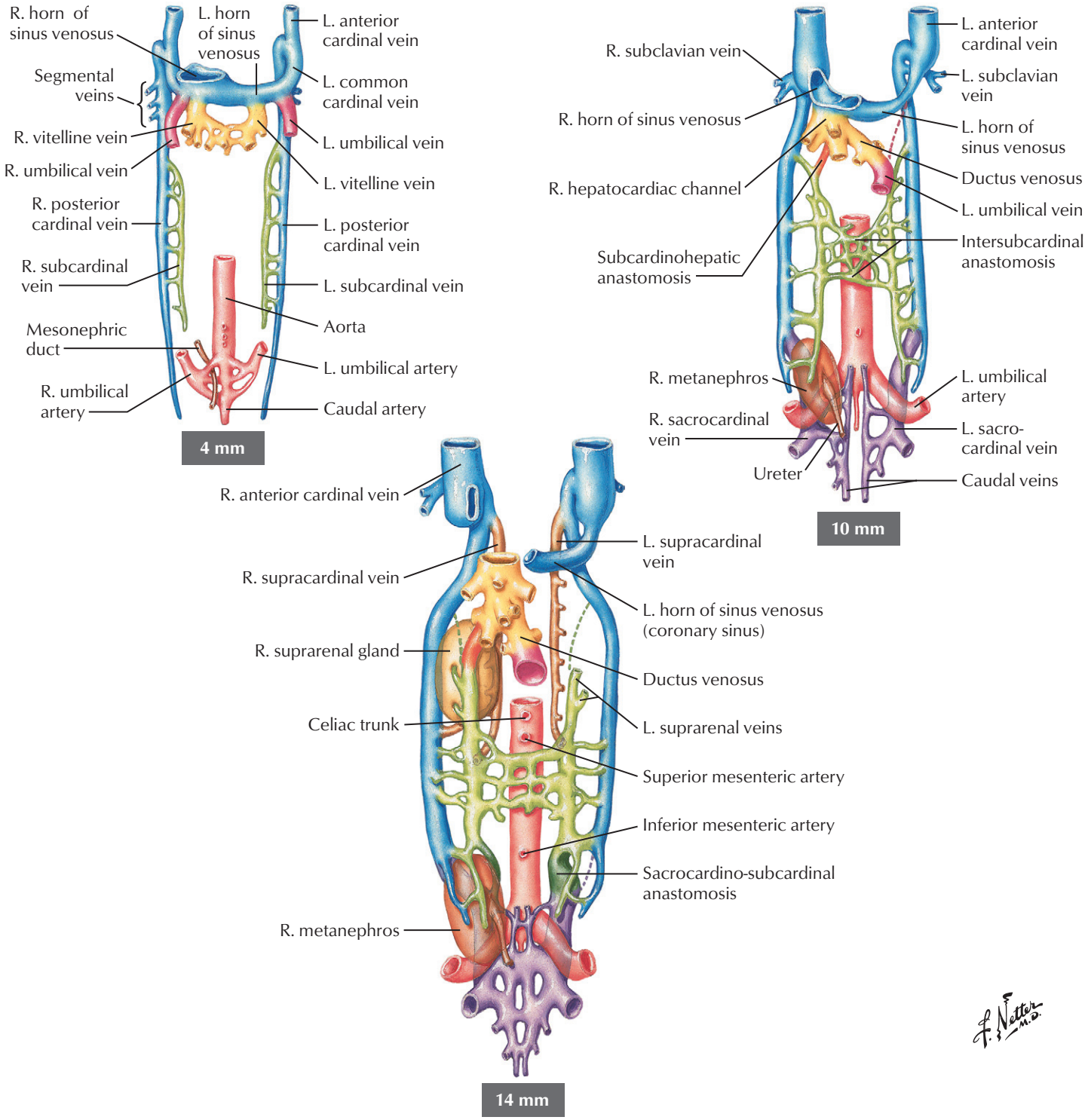


FIGURE 4.2 EARLY DEVELOPMENT OF THE CARDINAL SYSTEMS

The cardinal, subcardinal, and supracardinal veins develop and interconnect in temporal sequence, forming the **intraembryonic cardinal system of veins.** Anterior cardinal veins become the veins cranial to the heart. Supracardinal veins relate to the late-growing thoracic wall. The major events occur in the abdomen, where the left and right posterior cardinal veins disappear, and blood from the lower half of the embryo shifts to the subcardinal veins. The right subcardinal vein will connect to the heart via the most proximal segment of the right vitelline vein that is forming the intrahepatic segment of the inferior vena cava, the hepatic veins, and the hepatic portal vein.

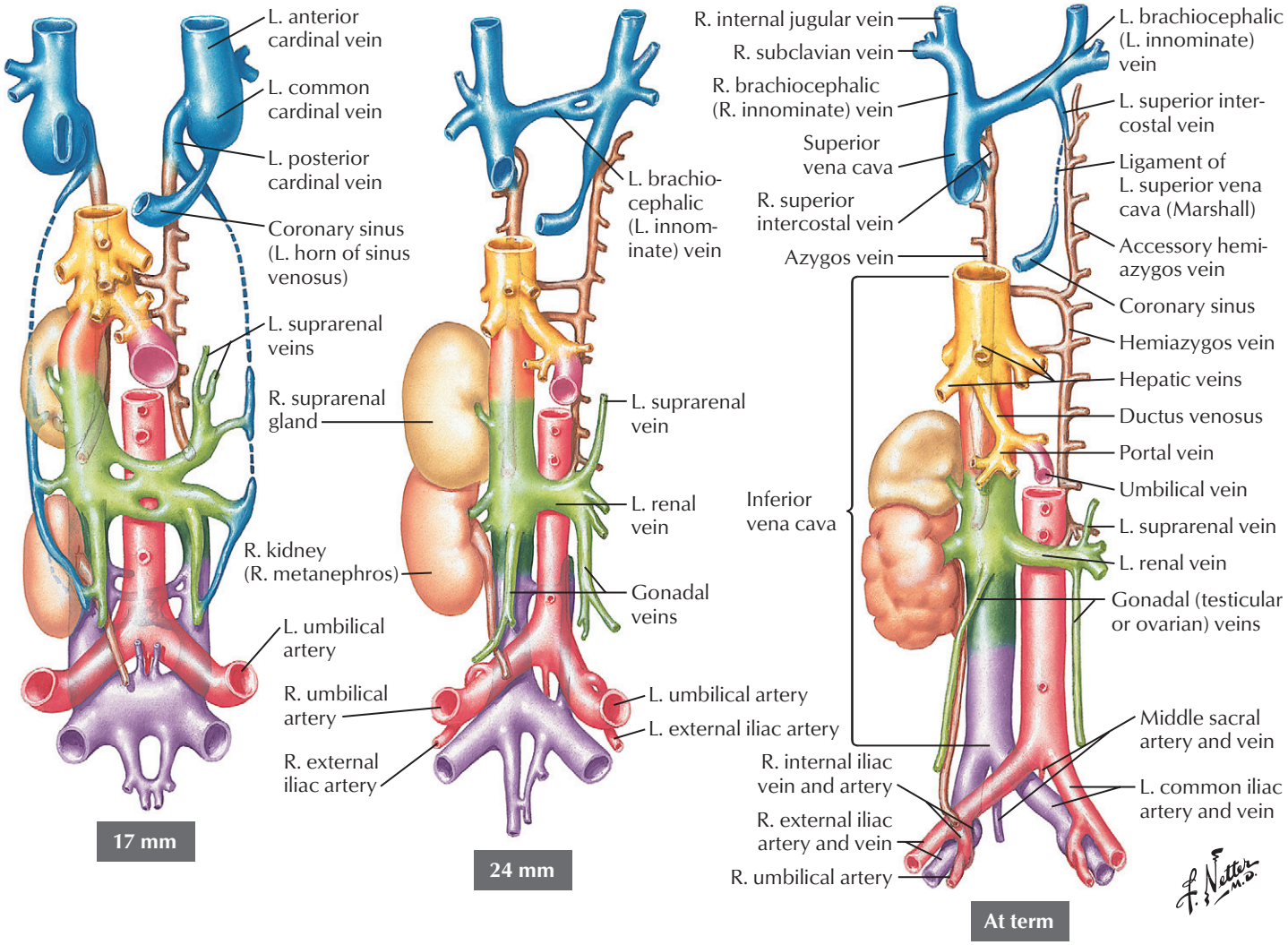


FIGURE 4.3 TRANSFORMATION TO THE POSTNATAL PATTERN

Blood from the pelvis and lower extremity converges on the developing common iliac veins. As the posterior cardinal veins diminish in size, the **subcardinal veins** connect to the common iliac veins and greatly enlarge on the right to form the **lower inferior vena cava.** They also form the **renal and gonadal veins.** The vitelline veins give rise to the upper, intrahepatic portion of the inferior vena cava. The veins of the abdominal viscera are related to the proximal vitelline veins because of the endodermal continuity of the yolk sac and midgut. The subcardinal portion of the inferior vena cava joins the portal and hepatic circulation by anastomosis with the vitelline veins on the right.

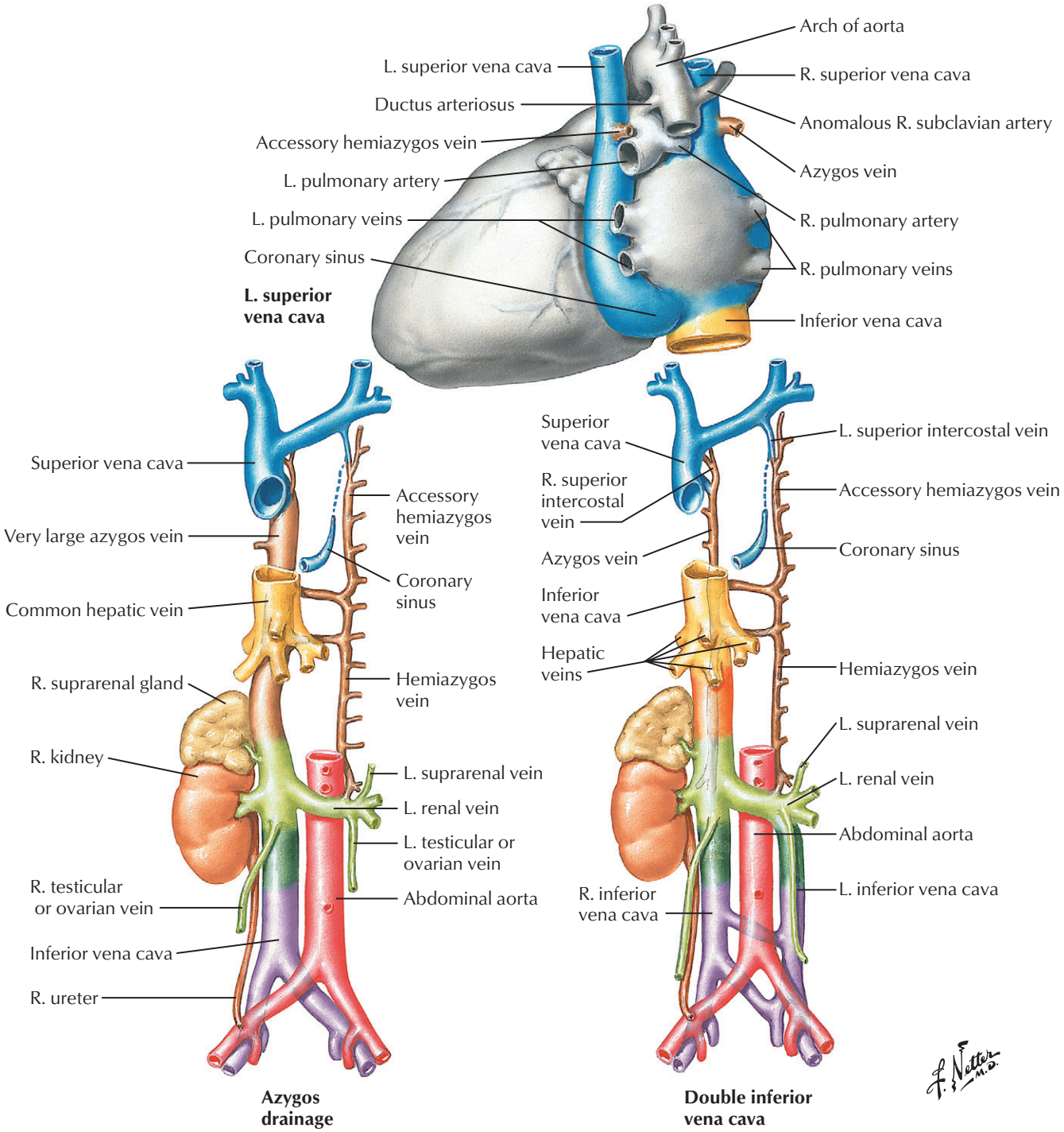


FIGURE 4.4 VEIN ANOMALIES

All three cardinal systems begin as paired veins of similar size. Later in fetal development the right side predominates as the superior and inferior vena cavae and related veins. The bilateral nature of the veins may persist as a double superior vena cava (top), inferior vena cava (bottom right), or both. The complicated sequences of venous development may result in abnormal connections. For example, if the anastomoses between the subcardinal and vitelline veins fail to develop, the lower inferior vena cava continues as the azygous vein, and the inferior vena cava entering the right atrium drains blood only from the gut via the hepatic veins and hepatic portal vein (bottom left).

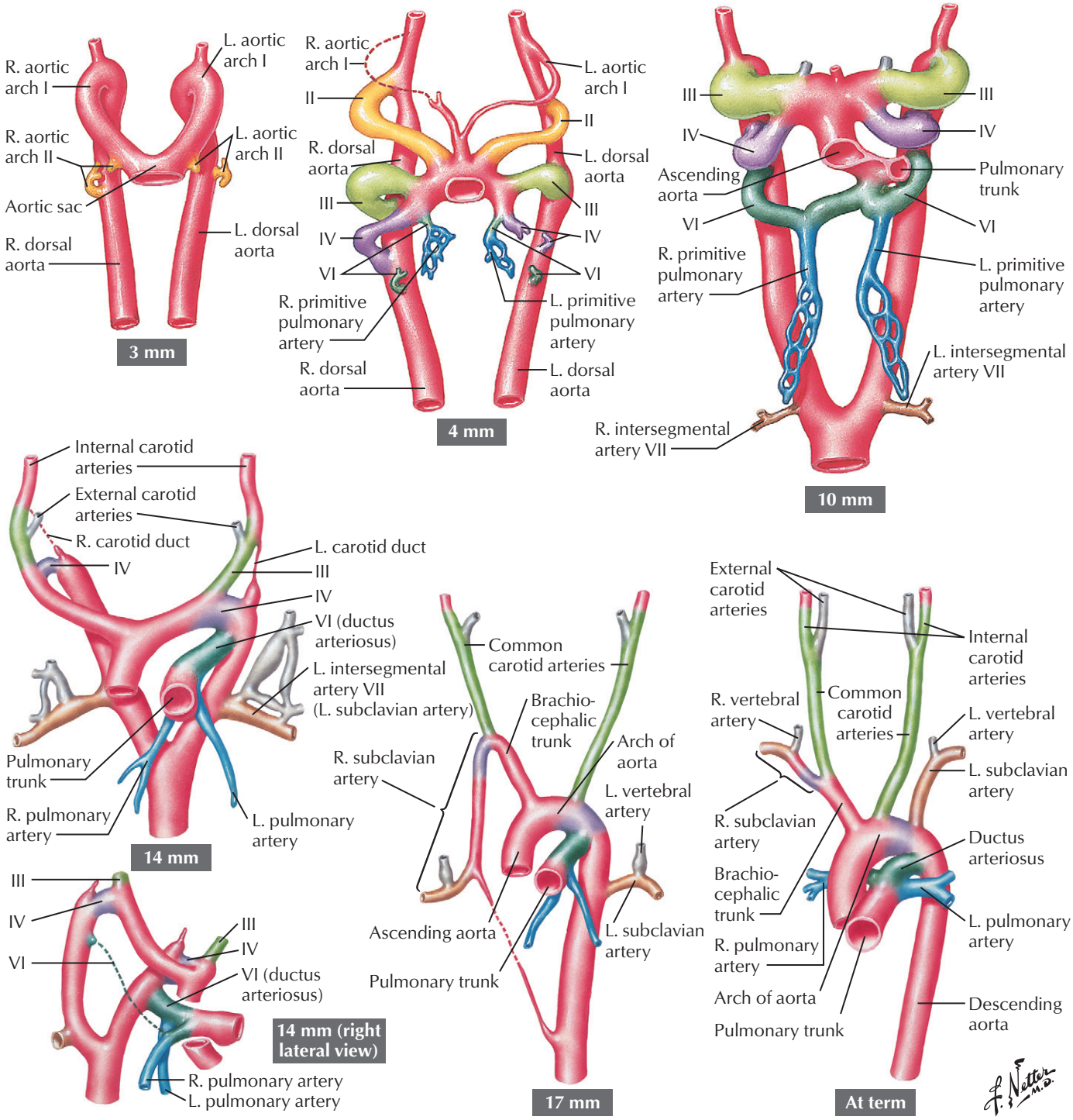


FIGURE 4.5 AORTIC ARCH ARTERIES

At the end of week 4, blood flows from the primitive heart to the tissues through a series of paired arteries that pass through the pharyngeal arches of mesoderm flanking the foregut. They connect to a left and right dorsal aorta that fuse into a single aorta caudal to the pharyngeal arches. The right dorsal aorta disappears as the aortic arches transform into adult pattern during the sixth week.

Major Aortic Arch Derivatives:
Arch 1: Mostly disappear but contribute to the maxillary arteries
Arch 2: Mostly disappear
Arch 3: Common and internal carotid arteries
Arch 4: Right subclavian artery and part of the arch of the aorta
Arch 6: Ductus arteriosus and proximal parts of the pulmonary arteries

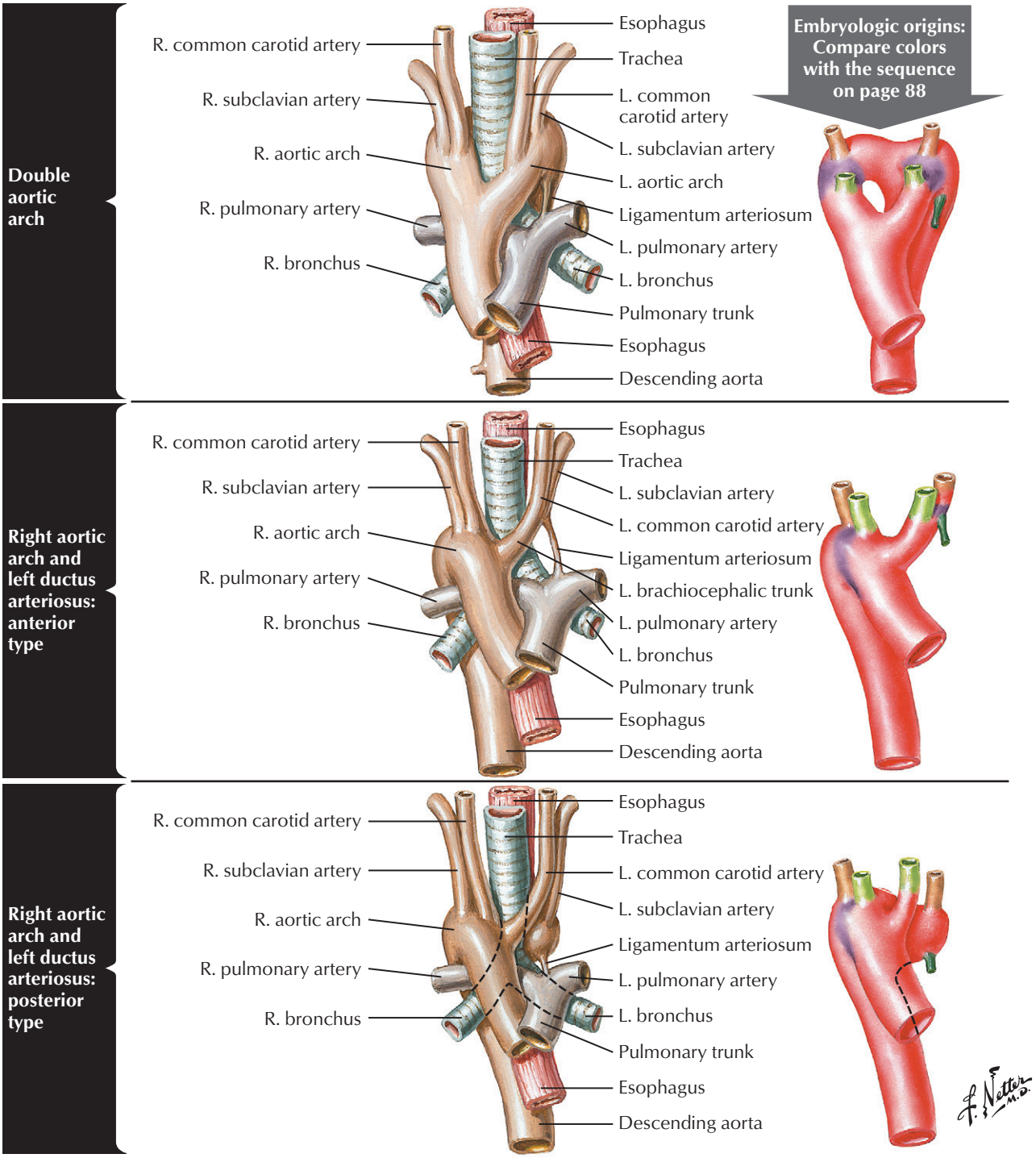


FIGURE 4.6 AORTIC ARCH ANOMALIES

A double aortic arch results when the initial connection between the aortic sac and the aortic arches on the right remain (top). A right aortic arch forms when this connection persists while the one on the left that forms the ascending aorta degenerates. Two variations of a right aortic arch are shown: one with the left subclavian artery passing in front of the trachea (middle) and one with it passing behind (bottom).

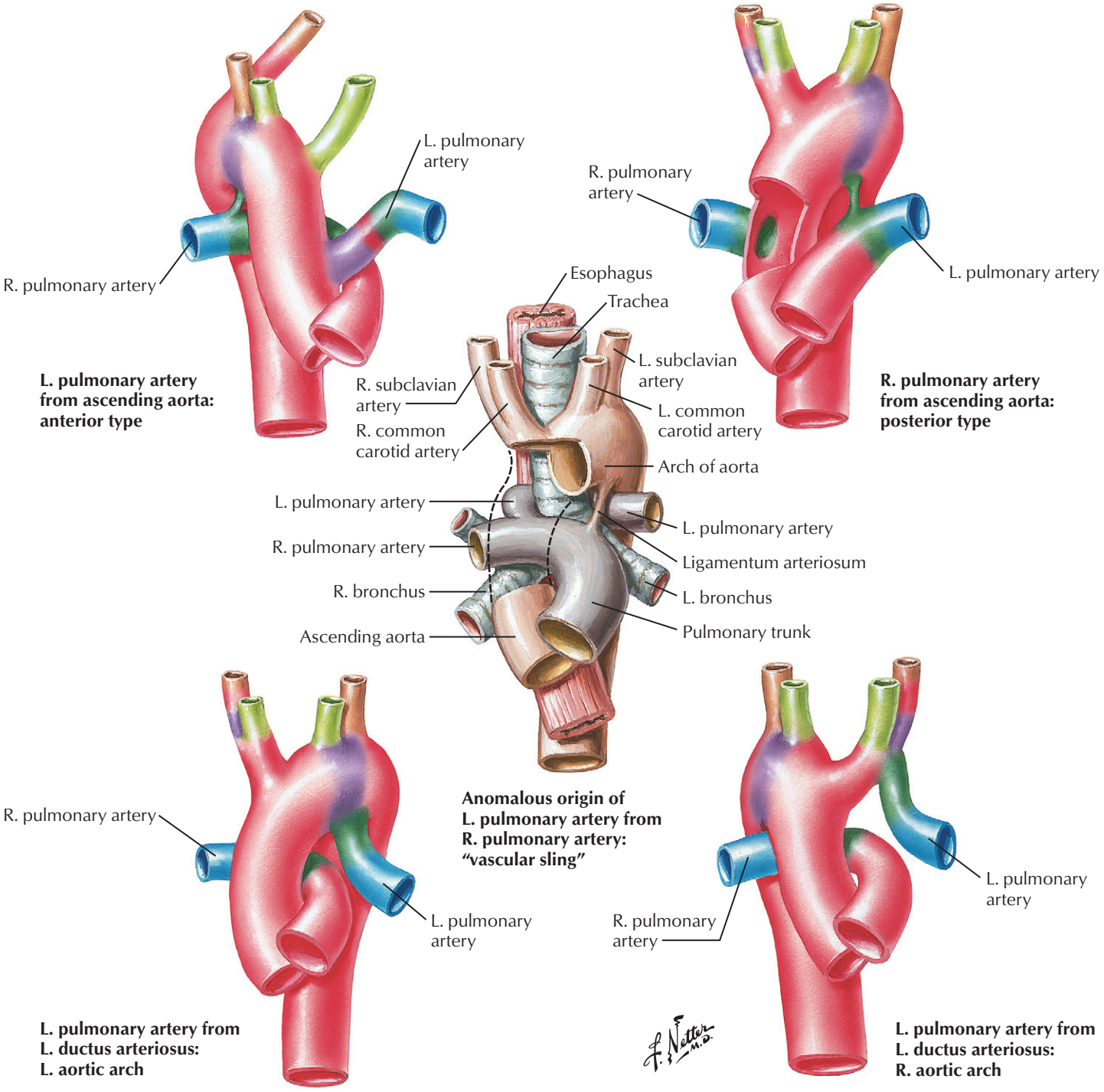


FIGURE 4.7 ANOMALOUS ORIGINS OF THE PULMONARY ARTERIES

The sequence of events in the transformation of the aortic arches is complex, and there are many opportunities for disruptions in the process. The pulmonary arteries and the ductus arteriosus develop from the most caudal pair of aortic arches (sixth), so the division of the truncus arteriosus into the ascending aorta and pulmonary trunk can affect their connections. Shown here are examples of a pulmonary artery originating from the ascending aorta, from a right aortic arch, from the inferior end of the ductus arteriosus, or from the opposite pulmonary artery.

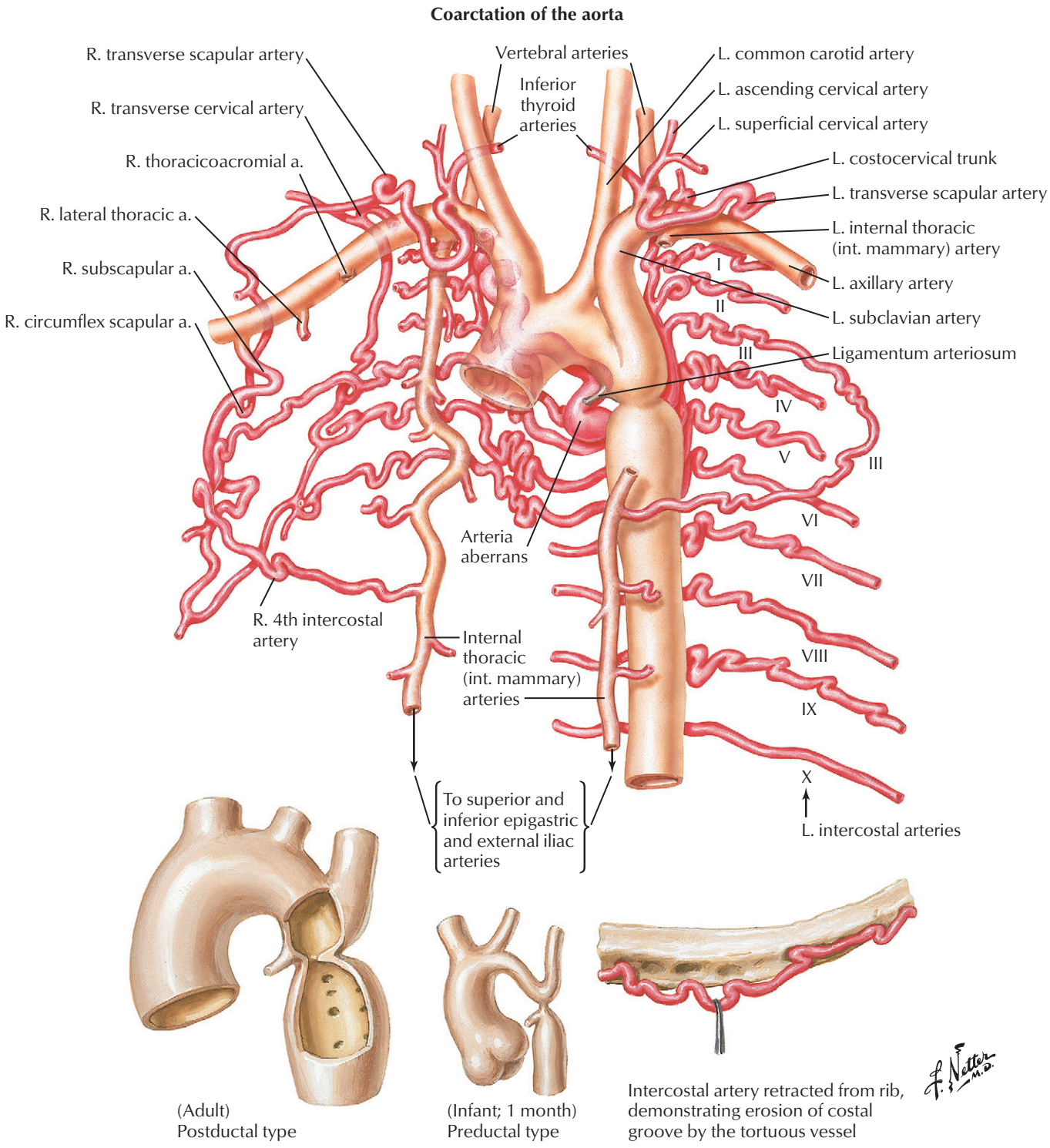


FIGURE 4.8 INTERSEGMENTAL ARTERIES AND COARCTATION OF THE AORTA

Coarctation of the aorta is a congenital narrowing that occurs near the entrance of the ductus arteriosus. Blood flows through two collateral routes in the internal thoracic arteries to get to the lower body: (1) the deep superior and inferior epigastric arteries into the external iliac and (2) intercostal arteries with retrograde flow into the thoracic aorta. The intercostal arteries are dilated and tortuous from the increase in blood pressure and flow. Most of the somatic arteries of the trunk develop, at least in part, from **intersegmental arteries** from the dorsal aorta. They pass between each of the somites and contribute to the vertebral, subclavian, intercostal, lumbar, common iliac, and lateral sacral arteries.

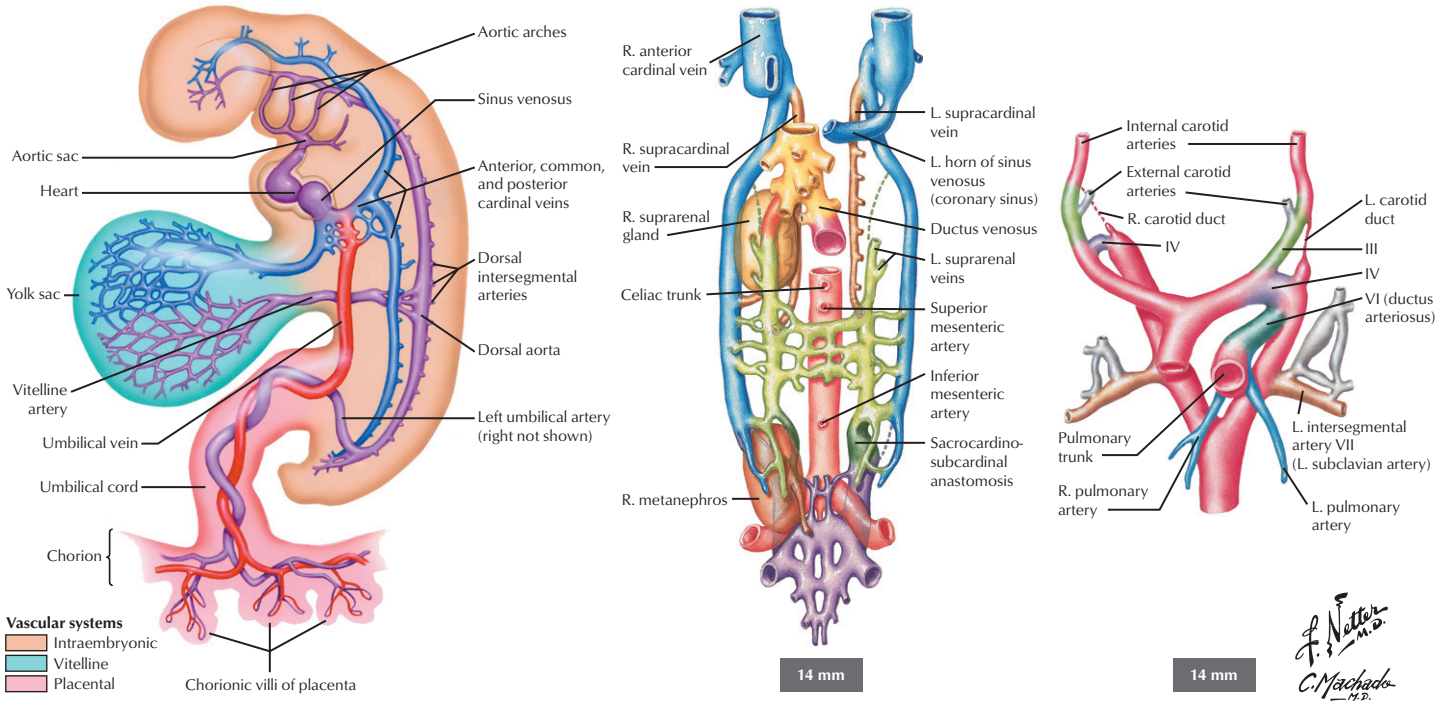


CHART 4.1 EMBRYONIC BLOOD VESSEL DERIVATIVES

Embryonic Vessels	Major Derivatives
Aortic arch artery 1	Part of maxillary arteries
Aortic arch artery 3	Common and internal carotid arteries
Aortic arch artery 4	Right subclavian artery; part of aortic arch
Aortic arch artery 6	Ductus arteriosus; proximal pulmonary arteries
Intersegmental arteries	Intercostal arteries Lumbar arteries Common iliac arteries Parts of vertebral, subclavian, and lateral sacral arteries
Umbilical arteries	Medial umbilical ligaments on the internal aspect of the abdominal wall
Umbilical vein	Round ligament of the liver (ligamentum teres)
Vitelline arteries	Celiac trunk Superior mesenteric artery Inferior mesenteric artery
Vitelline veins	Hepatic portal system Hepatic veins Intrahepatic segment of the inferior vena cava
Anterior cardinal veins	Superior vena cava Brachiocephalic (innominate) veins Internal jugular veins
Subcardinal veins (and anastomoses between the systems)	Lower inferior vena cava Renal and suprarenal veins Gonadal veins
Supracardinal veins	Azygous system of veins Segment of the inferior vena cava between the kidneys and liver

FIGURE 4.9 SUMMARY OF EMBRYONIC BLOOD VESSEL DERIVATIVES

The umbilical vessels become fibrous ligaments. The development of gastrointestinal vessels from the vitelline circulation reflects the close relationship between the endodermal yolk sac and gut tube. Veins cranial to the heart come from the anterior cardinal veins. Veins below the liver (lower IVC, renal, gonadal) develop from the subcardinal system, and veins of the thoracic wall arise from the supracardinal veins. The aortic arch arteries form the arteries between the maxillary artery (arch 1) in the head and pulmonary arteries/ductus arteriosus in the mediastinum (arch 6). Halfway in between are the common carotid arteries that develop from the middle arch 3.

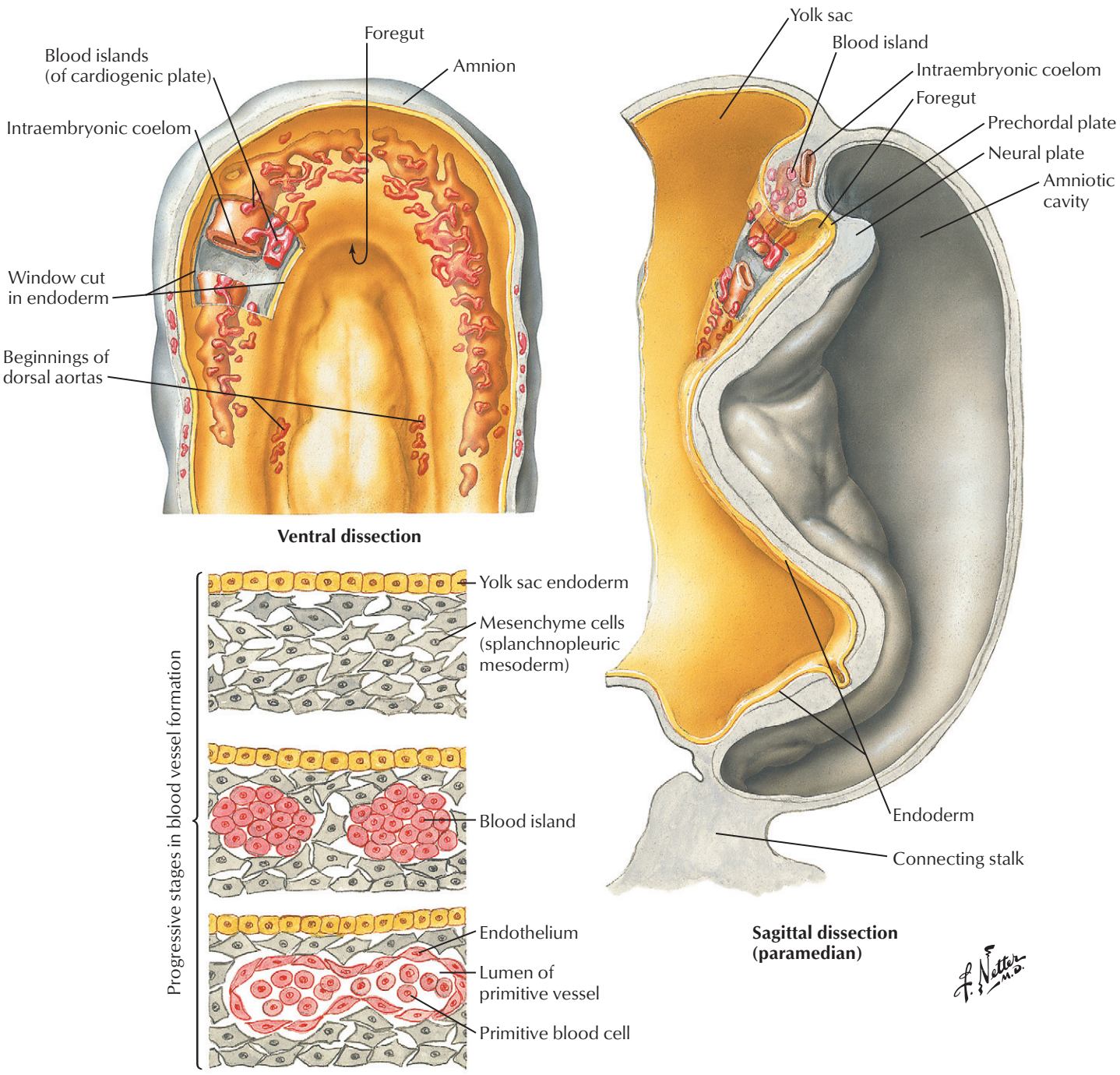


FIGURE 4.10 FORMATION OF BLOOD VESSELS

Blood vessels first appear next to the intraembryonic coelom in the lateral plate and cardiogenic mesoderm and in the extraembryonic mesoderm of the yolk sac and connecting stalk. Mesenchyme condenses into interconnecting cords of cells that cavitate to form the vascular lumen. Some mesenchymal cells remain within the lumen to differentiate into primitive blood cells near the end of week 3. The yolk sac and allantois are the first sources of embryonic blood cells. The fetal liver and spleen take over this function, with postnatal hemopoiesis occurring primarily in the bone marrow.

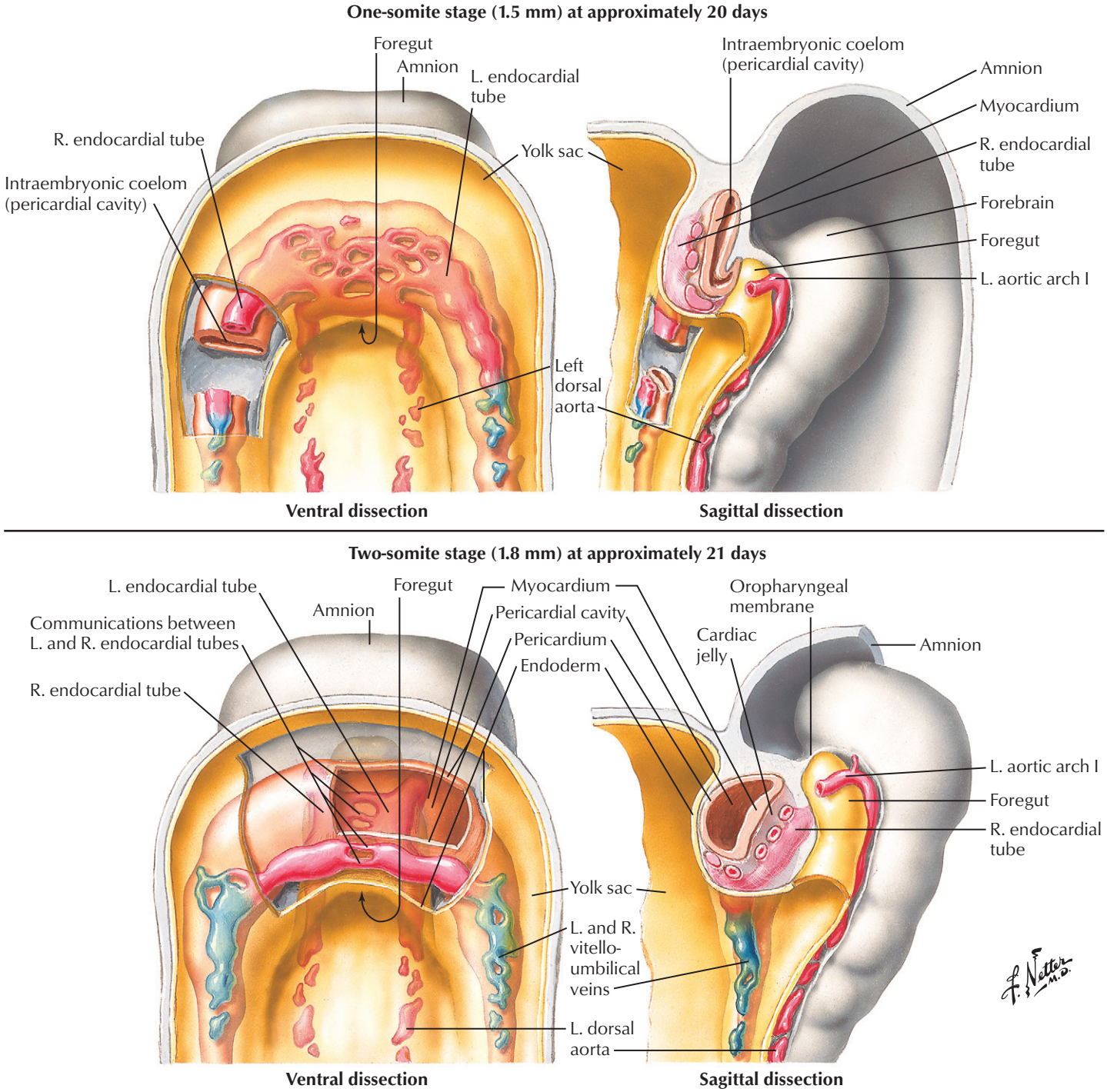


FIGURE 4.11 FORMATION OF THE LEFT AND RIGHT HEART TUBES

Vascular spaces coalesce into left and right heart tubes that begin to communicate with each other in the midline. Cardiogenic mesoderm adjacent to the heart tubes differentiates into a jellylike layer of connective tissue surrounded by a layer of muscle cells (myocardium). Ventral to the heart tubes, the cardiogenic mesoderm forms a cavity that is continuous with the intraembryonic coelom in the lateral plate mesoderm on both sides. By the beginning of the fourth week, peristaltic waves of contraction move blood through the embryonic tissues via aortic arch arteries surrounding the foregut, a left and right dorsal aorta, and the developing embryonic vasculature.

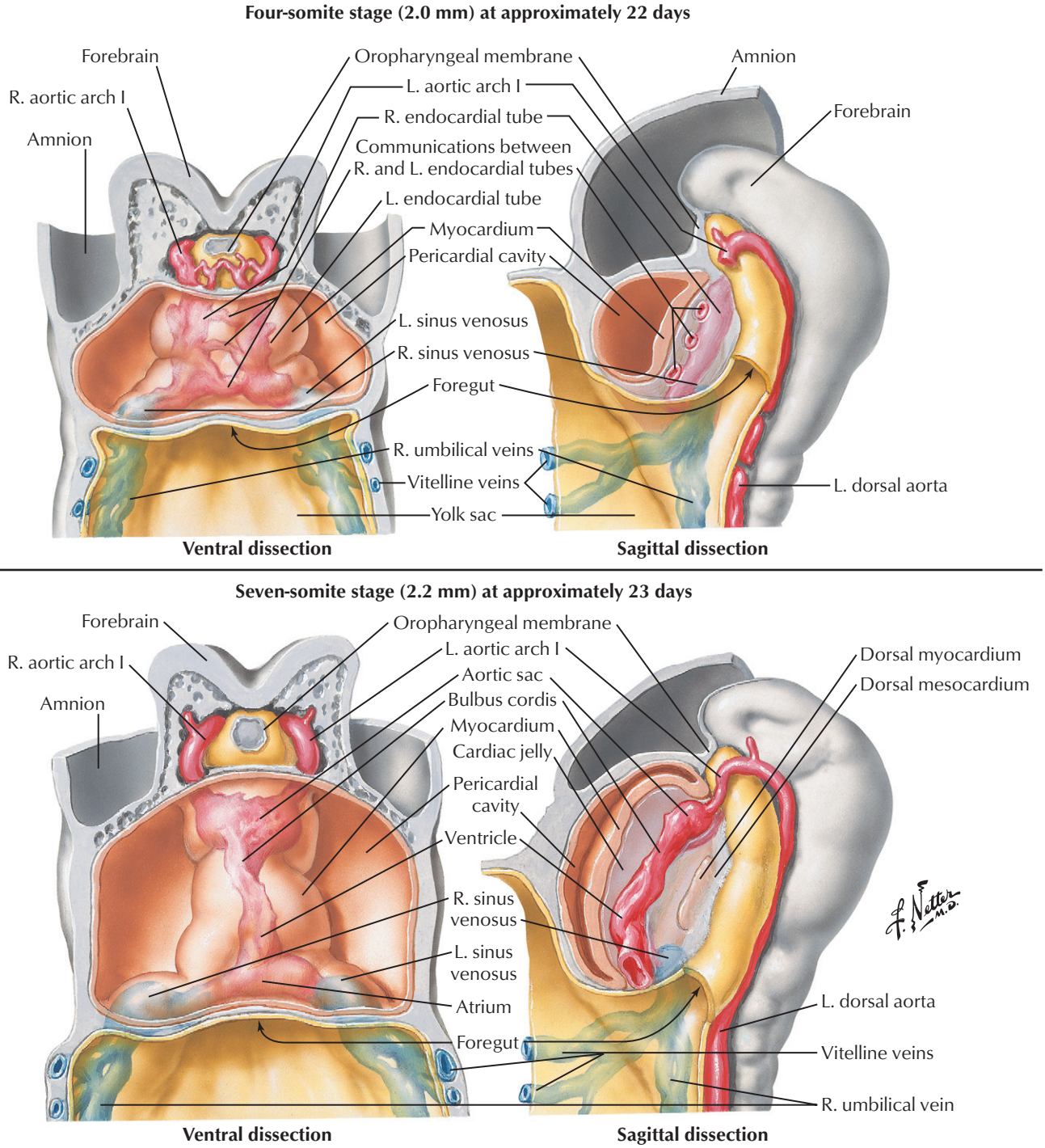


FIGURE 4.12 FORMATION OF A SINGLE HEART TUBE

The left and right heart tubes fuse into a single epithelial tube surrounded by an acellular layer of **cardiac jelly** and **mantle layer** that forms the heart muscle **(myocardium).** The enlarging tube sinks into the primitive pericardial coelom (cavity) and is suspended by a mesentery, the **dorsal mesocardium.** Epithelial cells from the cardiac mesoderm on the sinus venosus migrate over the myocardium to form the epicardium (visceral pericardium).

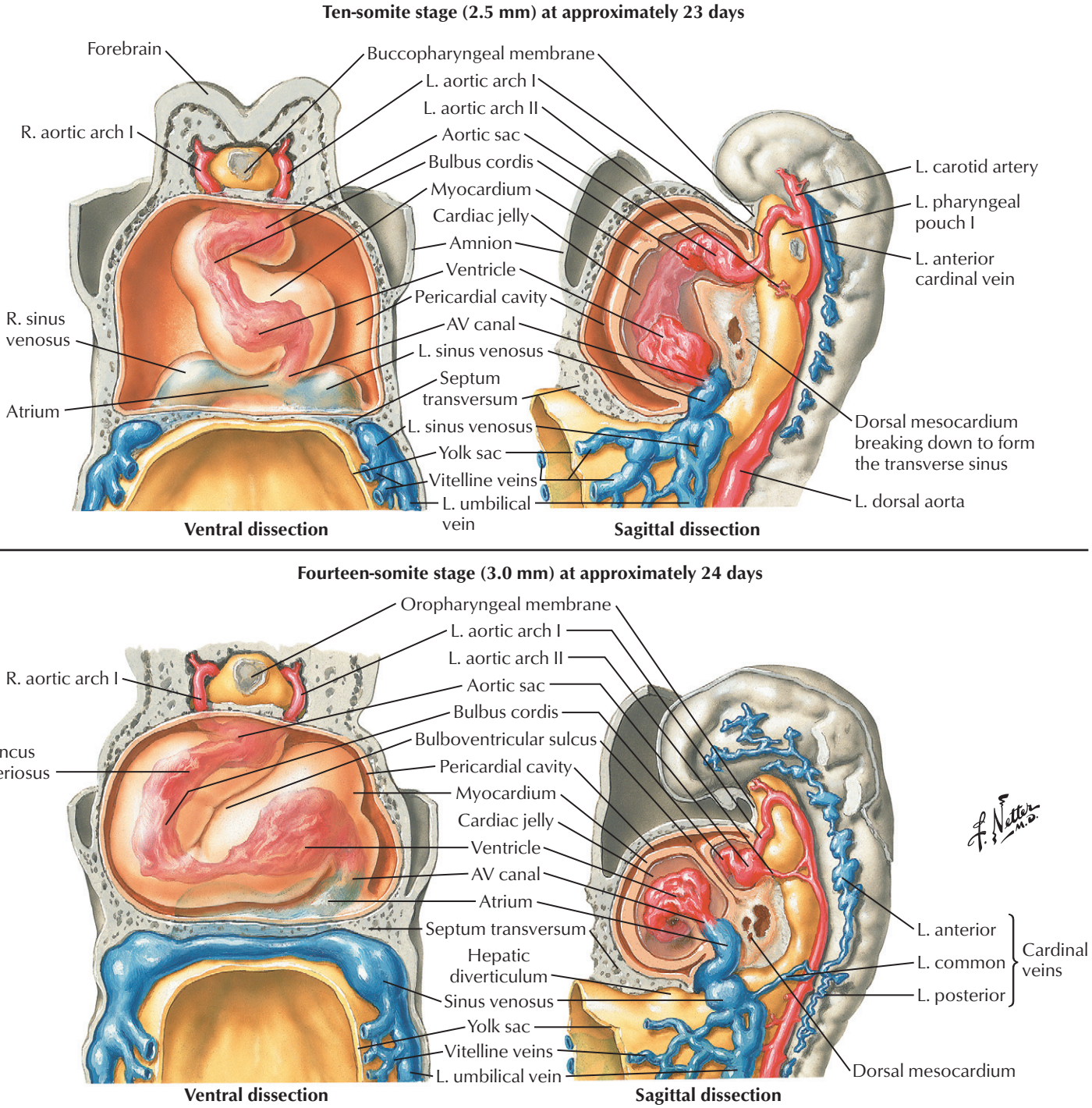


FIGURE 4.13 CHAMBERS OF THE HEART TUBE

Blood flows through a sequence of chambers in the single heart tube. From the venous end to the arterial end they consist of the **sinus venosus, atrium, ventricle, bulbus cordis, truncus arteriosus,** and **aortic sac** that gives rise to the aortic arches. The heart tube bends between the ventricle and bulbus cordis, and the venous end of the heart moves cranially behind the arterial part of the tube. The **dorsal mesentery** breaks down to form the **transverse sinus,** the space at the top of the heart between the great arteries and veins. The single atrium and single ventricle begin to form left and right chambers.

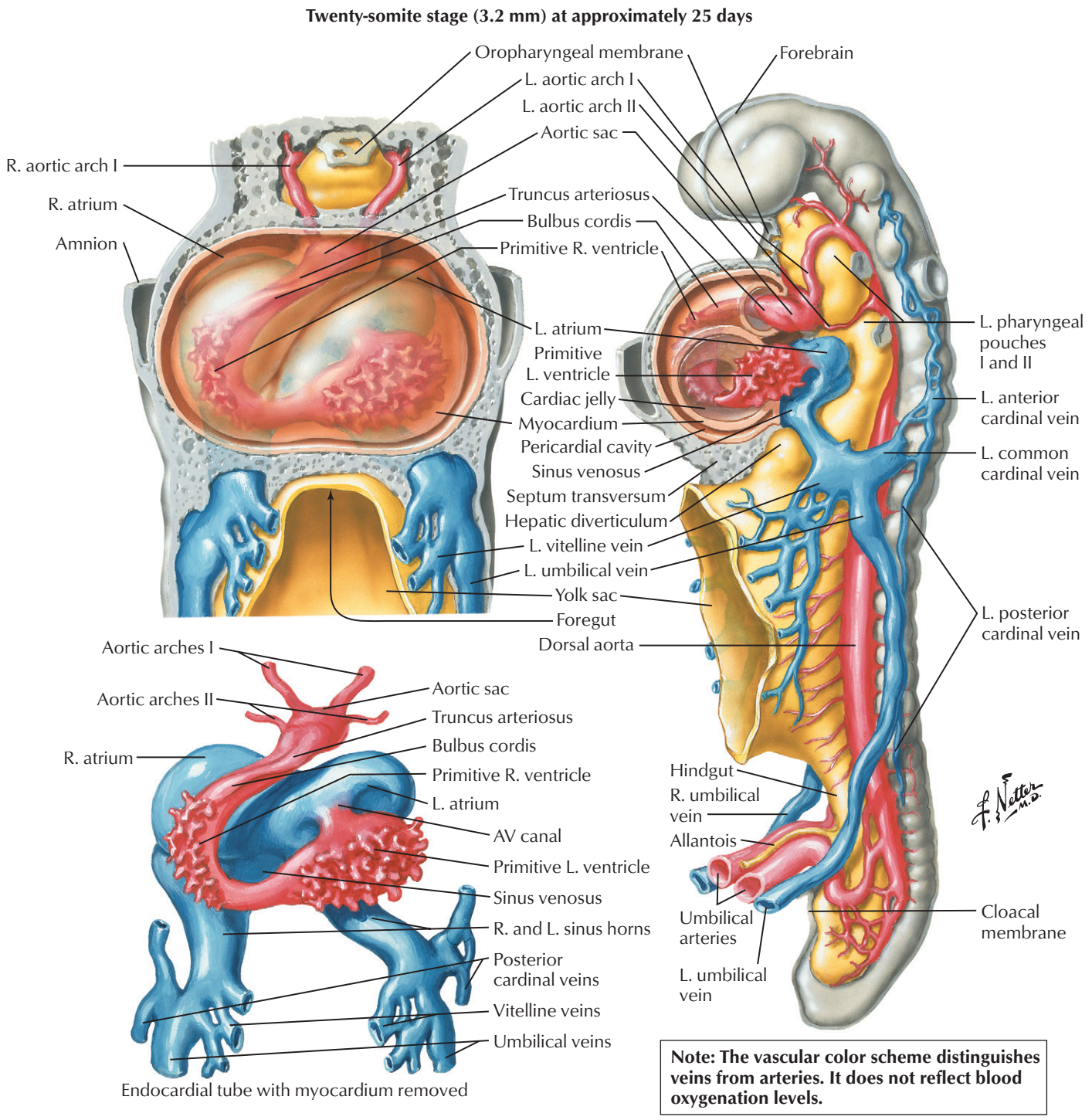


FIGURE 4.14 BENDING OF THE HEART TUBE

Blood flow is still in a single path through the primitive heart. The venous and arterial ends of the tube assume the dorsal/superior positions they occupy in the adult. Partitions begin to divide the single atrium and ventricle into left and right chambers. The three systems of veins converge on the sinus venosus leading into the heart tube: the common cardinal veins from embryonic tissues, the vitelline veins from the yolk sac, and the umbilical veins (soon to become one) from the placenta.

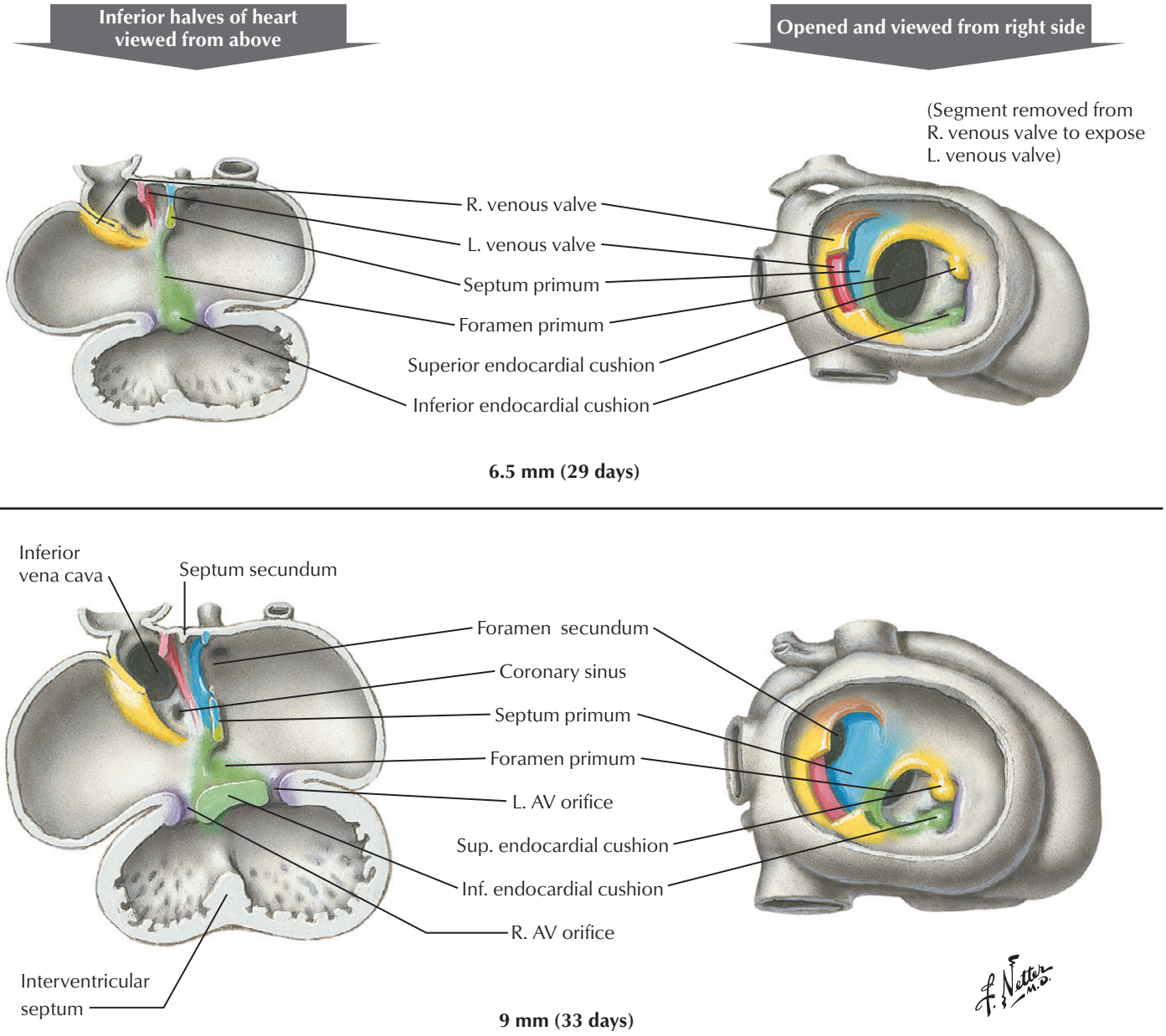
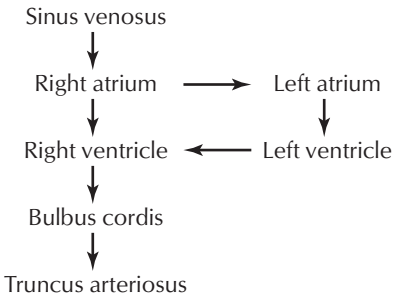


FIGURE 4.15 PARTITIONING OF THE HEART TUBE

Dorsal (superior) and ventral (inferior) **endocardial cushions** divide the atrioventricular canal (and blood flow) into left and right sides. An **interventricular septum** and a primary interatrial septum **(septum primum)** grow toward the endocardial cushions. The canal connecting the two atria is the **foramen primum.** As it diminishes in size with growth of the septum primum toward the endocardial cushions, the **foramen secundum** appears high up on the septum primum. A second interatrial septum, the **septum secundum,** develops on the right side of the septum primum.

After fusion of the endocardial cushions and the establishment of a left and right flow of blood, the heart still has one primary site of entry for blood (right atrium) and one primary site of exit (right ventricle). Blood must be able to pass between the atria and between the ventricles.



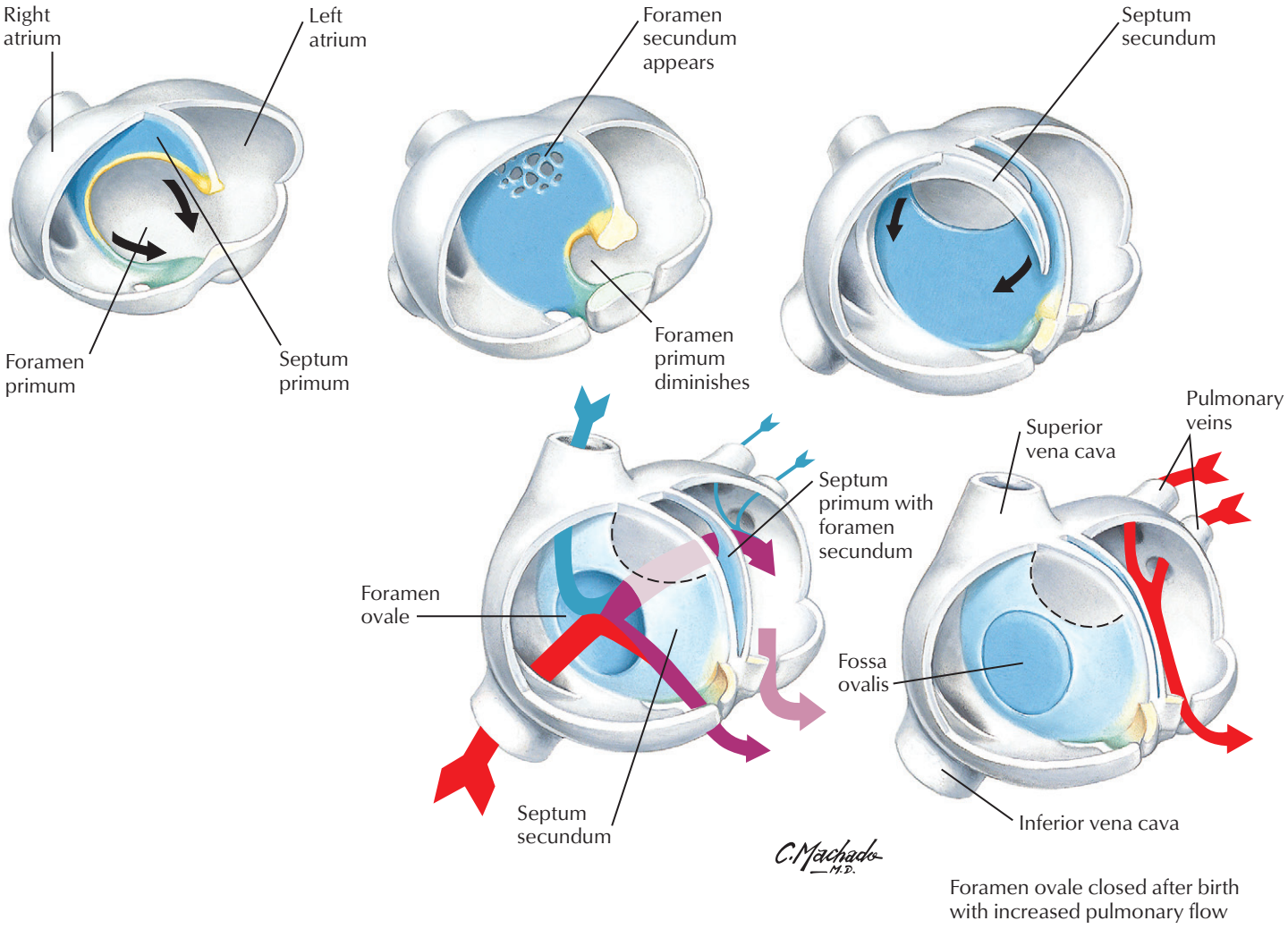


FIGURE 4.16 ATRIAL SEPARATION

The atria are divided by two septa: a septum primum with a foramen secundum and septum secundum with a foramen ovale. The foramen primum disappears as the septum primum grows toward and fuses to the endocardial cushions. The two foramina (secundum and ovale) are not aligned, and the two septa act as a simple valve permitting blood flow from right to left as blood from the inferior vena cava is directed toward the septum primum in the foramen ovale. When left atrial pressure rises at birth with the establishment of pulmonary blood flow, the septa are pushed together and the interatrial lung shunt is effectively closed.

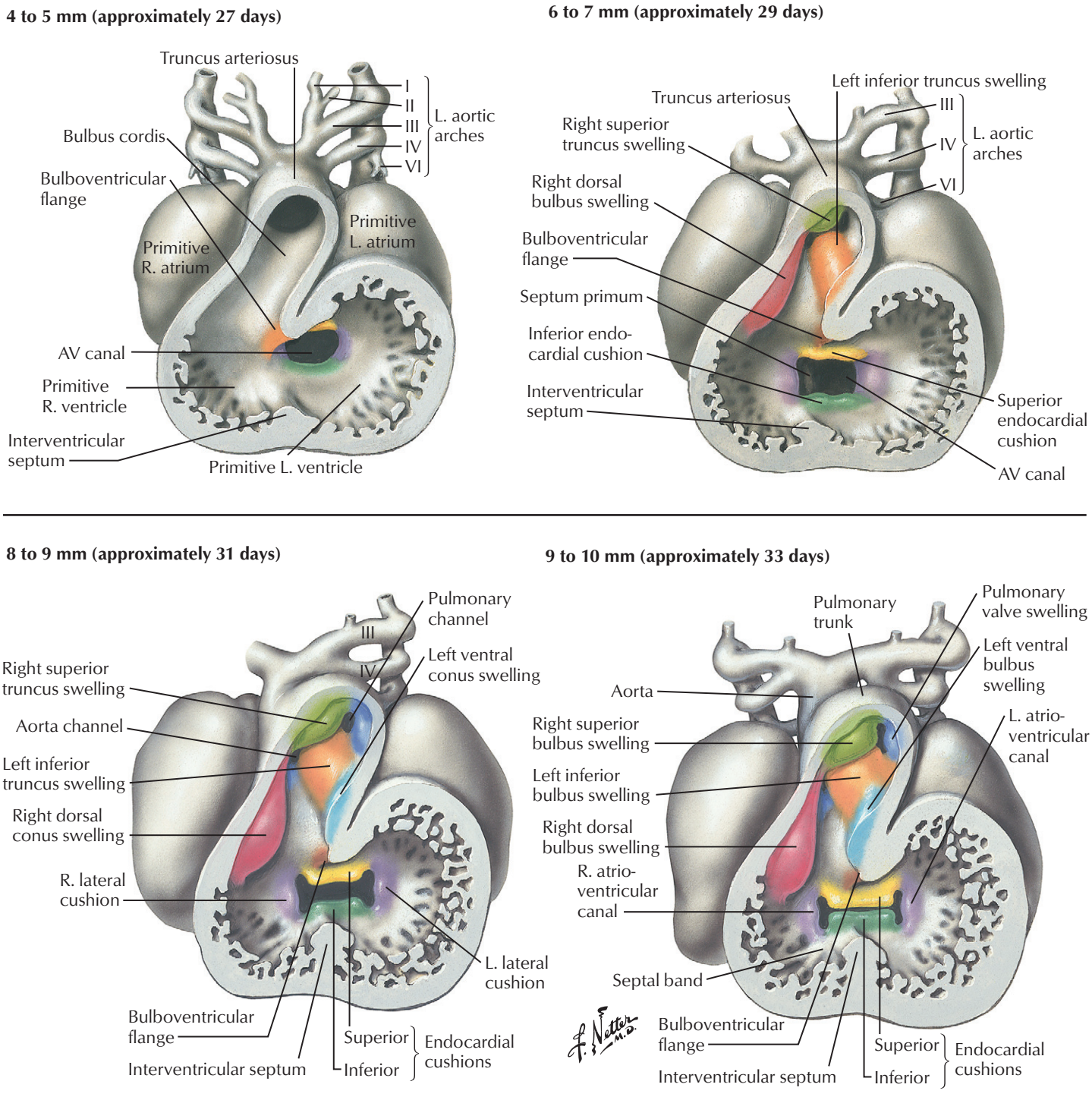


FIGURE 4.17 SPIRAL (AORTICOPULMONARY) SEPTUM

Division of the left and right ventricles is intimately related to division of the bulbus cordis and truncus arteriosus. The single ventricle begins to form left and right chambers with the appearance of the interventricular (IV) septum and the formation of the left and right atrioventricular canals by the superior and inferior (or dorsal/ventral) endocardial cushions. The division of the ventricles by the IV septum is not complete, and all blood exits the heart via the right ventricle, bulbus cordis, and truncus arteriosus. The blood takes a spiral path through these chambers, and ridges form a spiral septum between the streams. The septum is also called the aorticopulmonary septum because of the two arteries it forms from the truncus arteriosus.

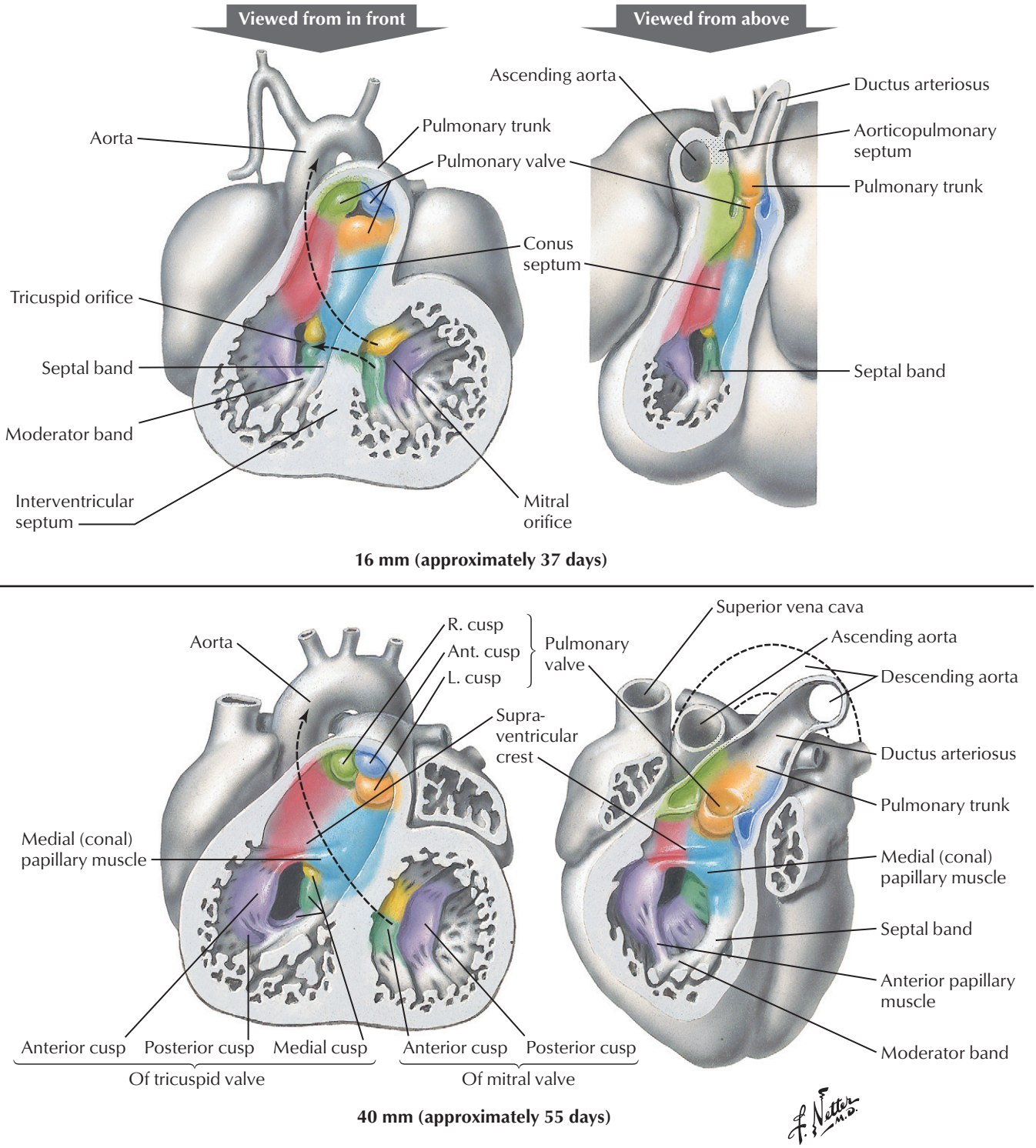


FIGURE 4.18 COMPLETION OF THE SPIRAL (AORTICOPULMONARY) SEPTUM

The longitudinal swellings in the outflow portion of the heart tube grow together to complete the spiral septum that divides the bulbus cordis and truncus arteriosus. The spiral septum fuses with the interventricular septum and endocardial cushions inferiorly to complete the division of the left and right ventricles. The **bulbus cordis** forms the smooth, upper portion of each ventricle below the semilunar valves (**aortic vestibule** in left ventricle, **conus arteriosus** in the right). The **truncus arteriosus** divides into the **ascending aorta** and **pulmonary trunk.** The latter connects to the aortic arch via the **ductus arteriosus,** the second shunt where blood bypasses the fetal lungs. Valve development is completed by 8 weeks.

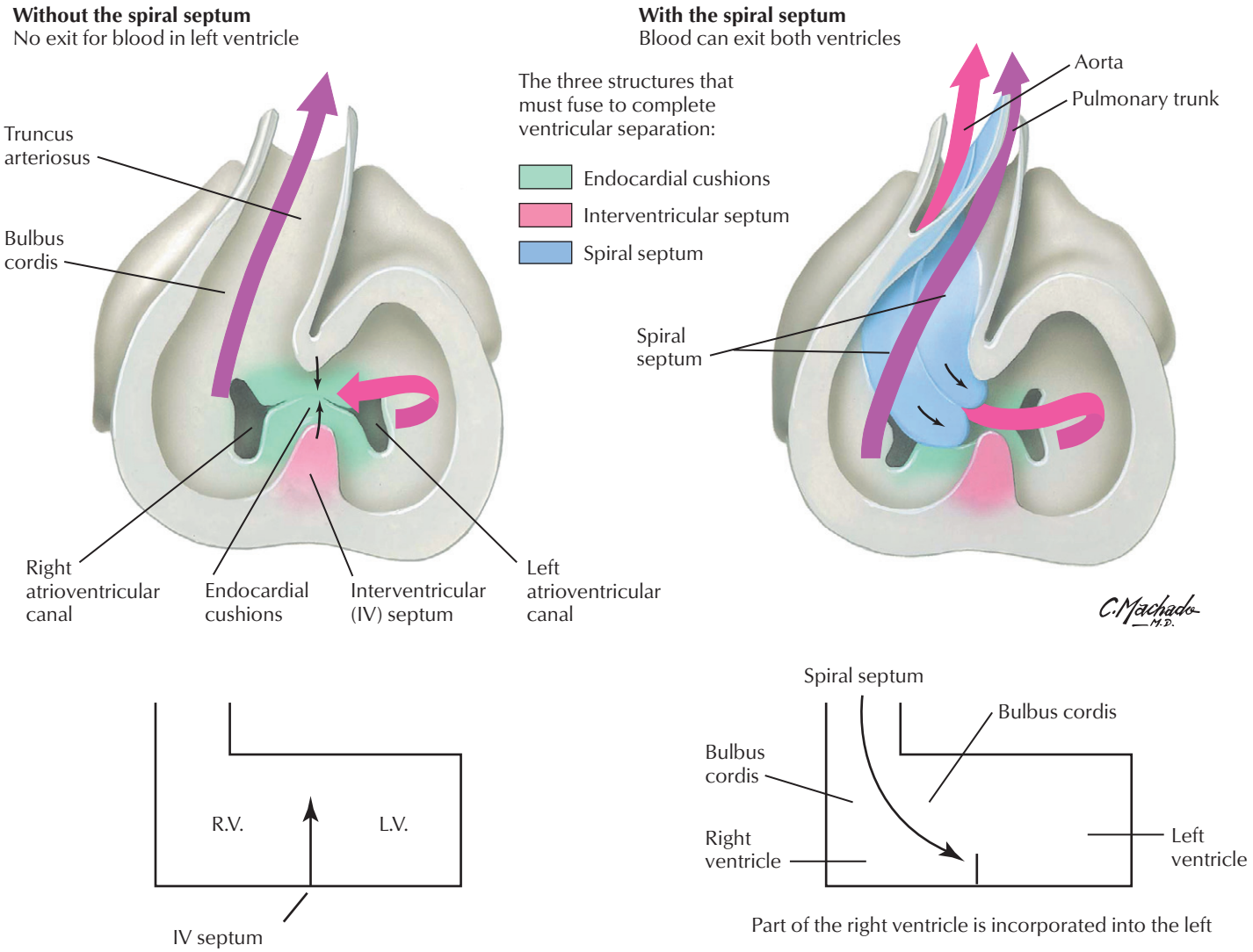


FIGURE 4.19 VENTRICULAR SEPARATION AND BULBUS CORDIS

The bulbus cordis and truncus arteriosus are continuations of the right ventricle. If the interventricular septum grew to the endocardial cushions to separate the ventricles, there would be no exit of blood from the left ventricle. Three primordia must fuse with each other to complete ventricular separation: the spiral septum, the interventricular (IV) septum, and the endocardial cushions. These structures form the upper, membranous part of the IV septum, the most common site of ventricular septal defects. The primary IV septum forms the lower muscular part. Because the spiral septum extends obliquely to the IV septum, part of the right ventricle gets incorporated into the left ventricle, and the bulbus cordis contributes to both chambers.

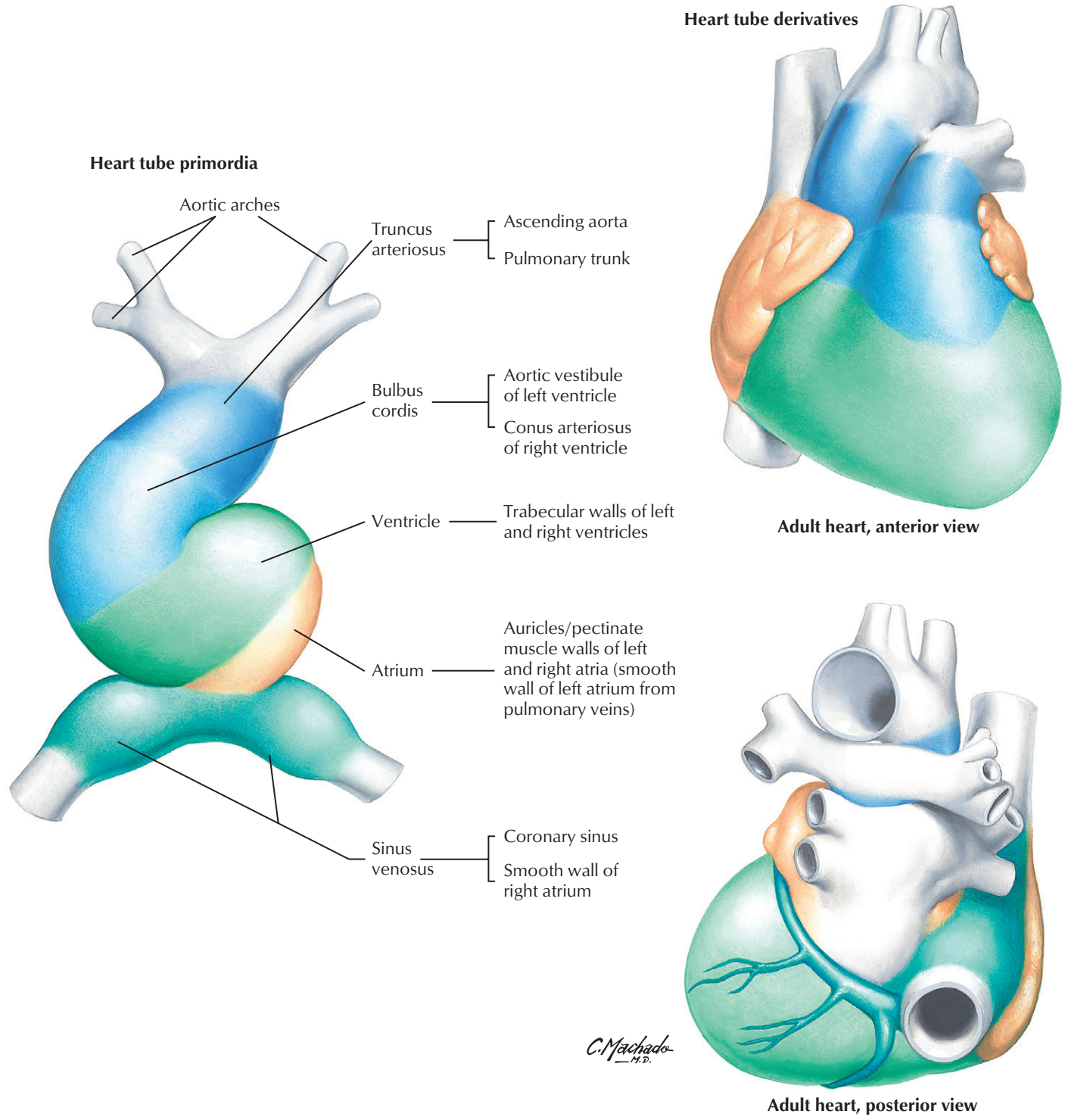


FIGURE 4.20 ADULT DERIVATIVES OF THE HEART TUBE CHAMBERS

The primitive heart tube (left) is color-coded according to the derivatives in the adult heart (right). The chambers of the heart are mostly lined with ridges of cardiac muscle, but the walls are smooth in both the inflow parts of the atria and outflow parts of the ventricles. The **primitive atrium** and **primitive ventricle** in the embryo give rise to the walls of the heart with ridged muscle, the **pectinate muscle** in the auricles of the atria and **trabeculae carneae** in the ventricles. The smooth posterior wall of the right atrium comes from the right horn of the sinus venosus. The smooth, outflow portion of both ventricles derives from the bulbous cordis. The smooth wall of the left atrium forms from a merging of the proximal portions of the pulmonary veins.

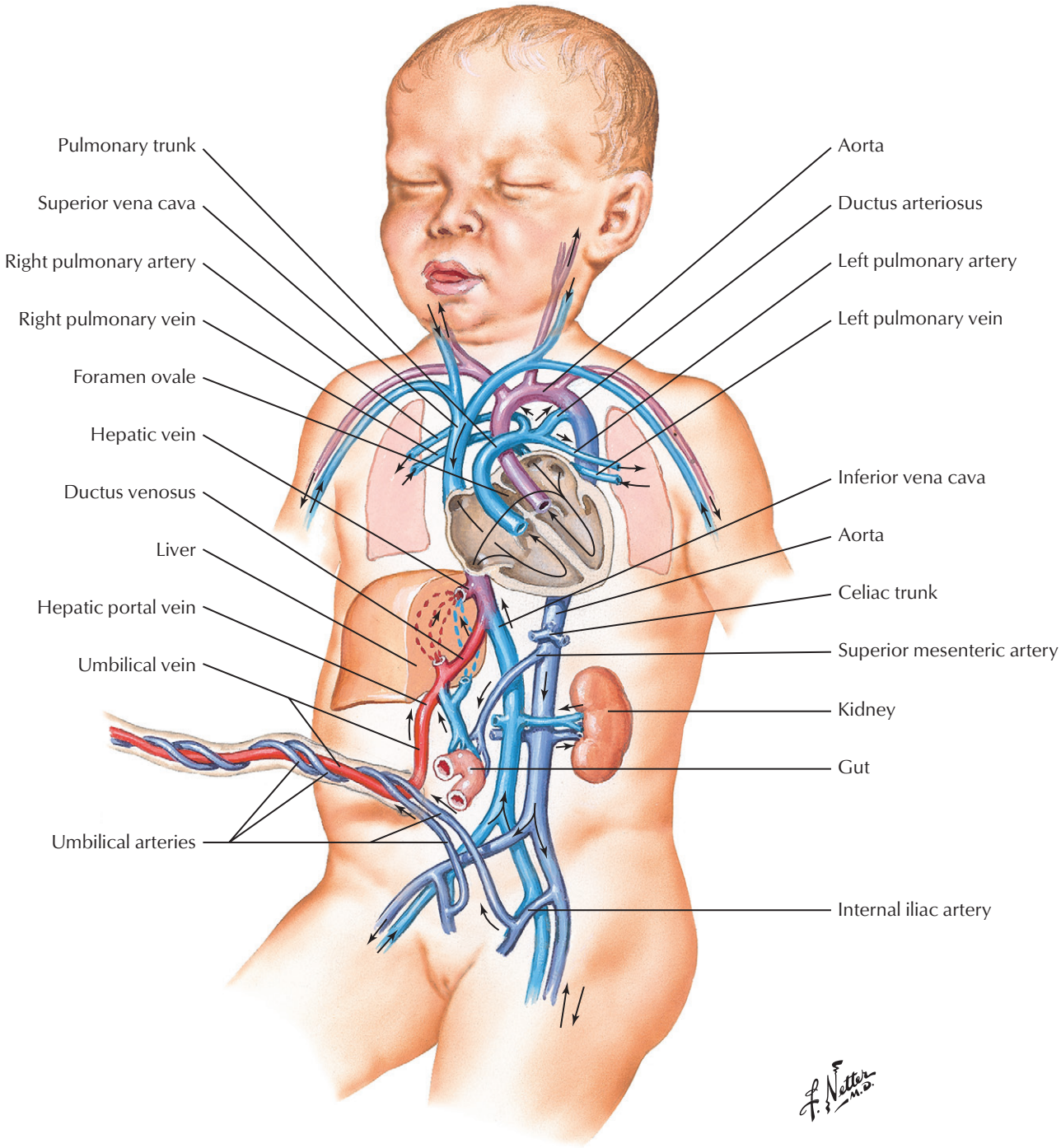


FIGURE 4.21 FETAL CIRCULATION

In prenatal circulation, oxygenated blood in the umbilical vein bypasses the liver via the **ductus venosus** and the lungs via two routes. Most blood from the inferior vena cava is directed toward the **foramen ovale** in the interatrial septum to flow to the left, systemic side of the heart. Most blood from the superior vena cava flows into the right ventricle and pulmonary trunk, where it is diverted from the pulmonary arteries into the lower-pressure aorta through the **ductus arteriosus.**

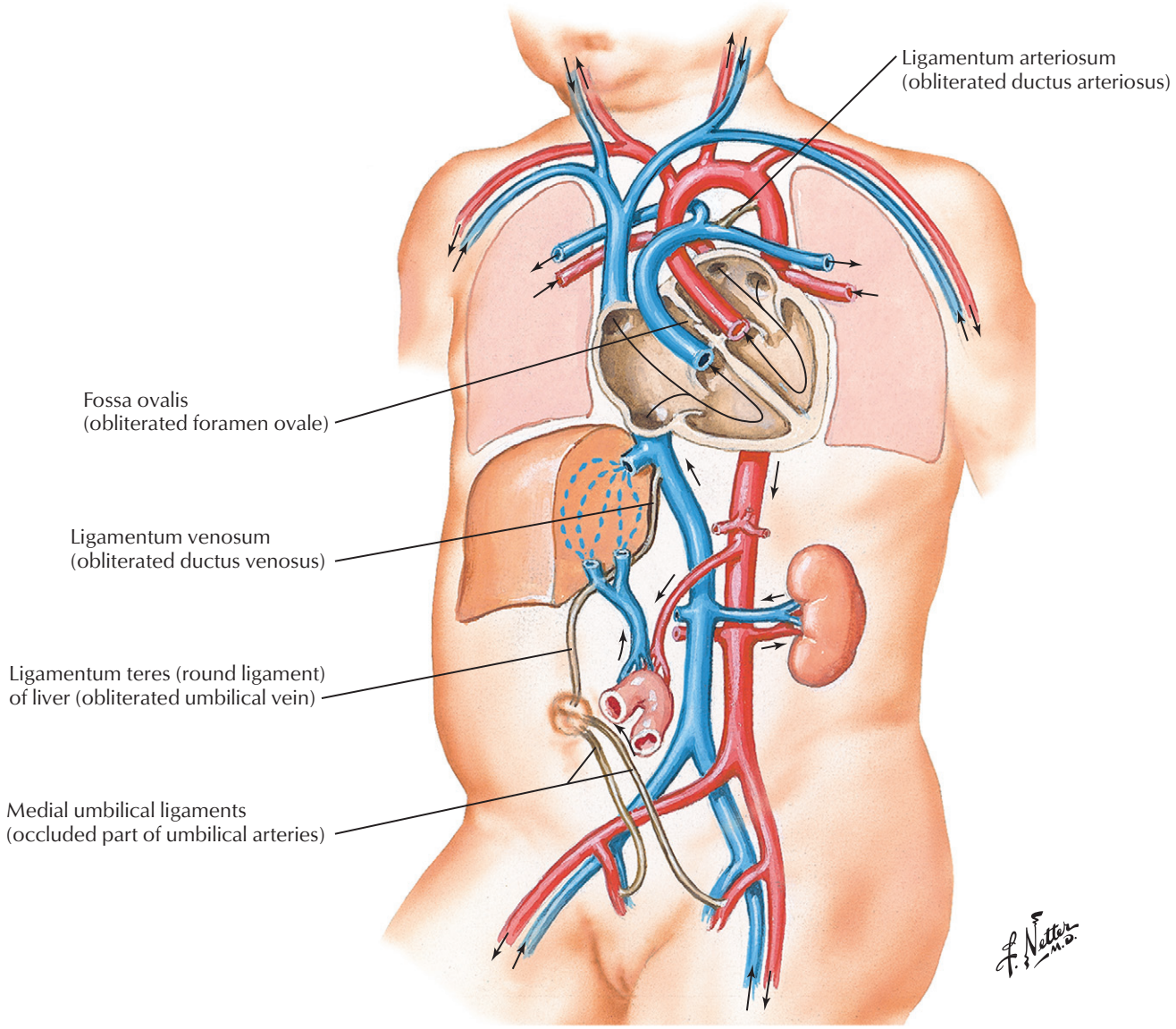
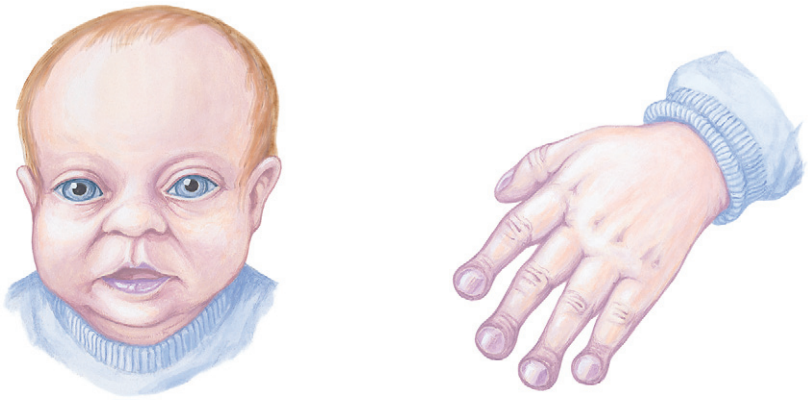


FIGURE 4.22 TRANSITION TO POSTNATAL CIRCULATION

Transition from fetal to postnatal circulation:

1. The first breath clears the airway of amniotic fluid, greatly reducing the pressure within the pulmonary vascular beds.
2. Lower pulmonary pressure causes blood to enter the lungs instead of passing through the ductus arteriosus to the aortic arch.
3. Blood rushes from the lungs into the left atrium, where the septum primum is pressed against the septum secundum to effectively close the foramen ovale.
4. Higher oxygen levels in the umbilical arteries cause them to spasm.
5. The uterus contracts, forcing most of the placental blood into the fetus. The umbilical vein collapses from lack of blood.

Clinical characteristics of too little pulmonary flow



Cyanosis

Clubbing of fingers

Clinical characteristics of too much pulmonary flow (pulmonary volume overload)

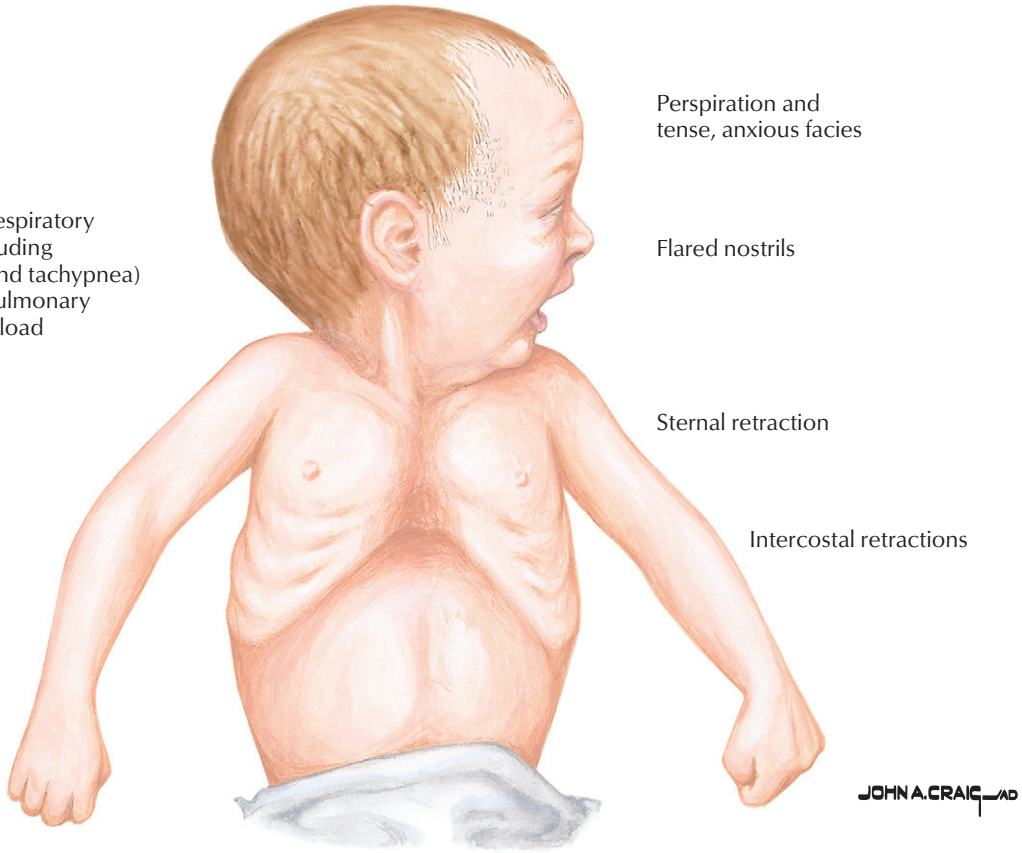


FIGURE 4.23 CONGENITAL HEART DEFECT CONCEPTS

Congenital heart defects result in problems if the lungs get too much or too little blood. Too little blood in the lungs may be caused by pulmonary stenosis or right ventricular outflow obstruction, in which case not enough blood is oxygenated to meet the metabolic demands of the body. Too much blood to the lungs results in excessive pulmonary return to the heart, which may overload the left atrium, left ventricle, and mitral valve. Blood backs up in the lungs, and fluid accumulates. This type of congestive heart failure is usually caused by abnormal communication between the high-pressure ventricles or great arteries.

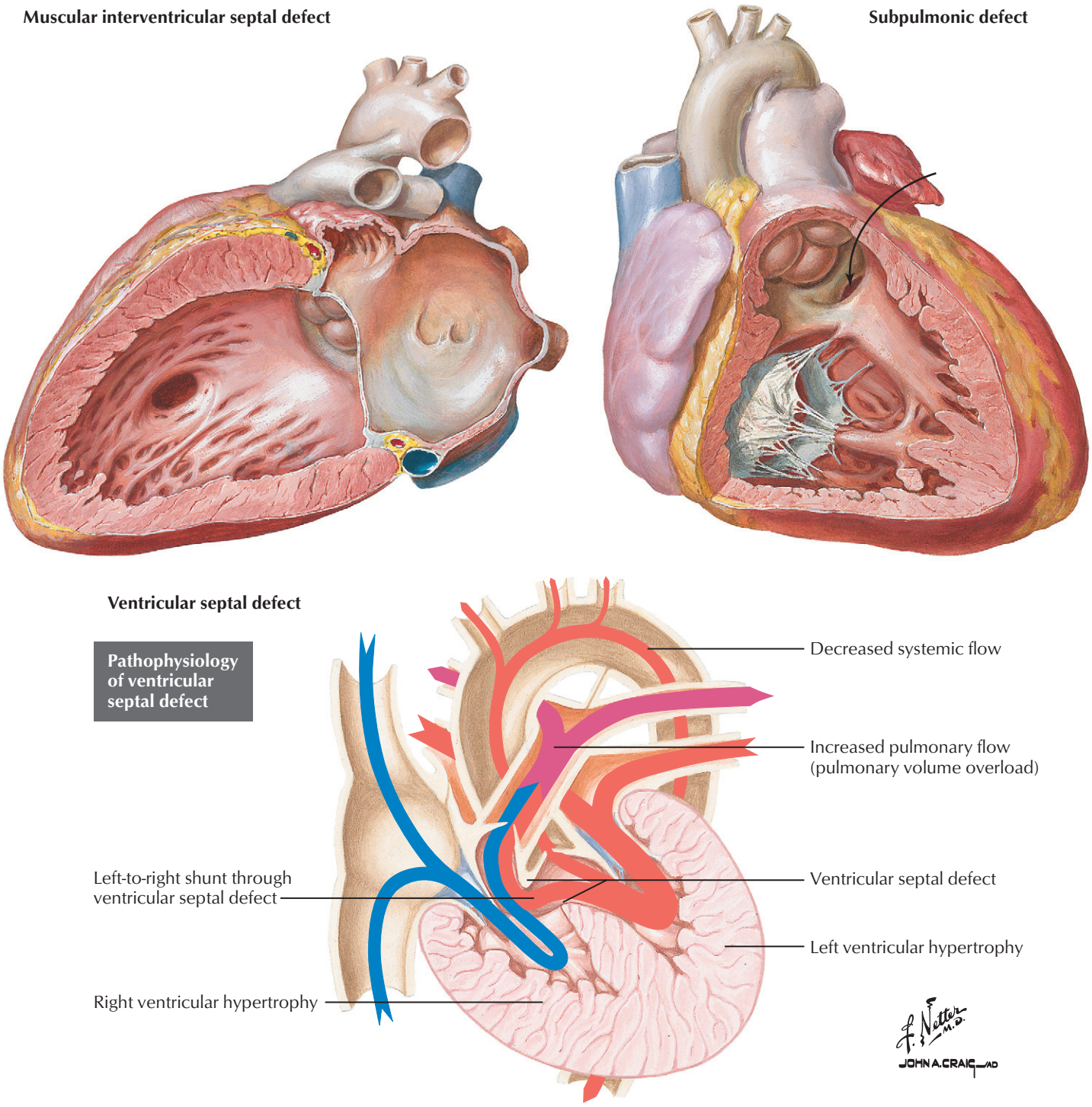


FIGURE 4.24 VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects (VSDs) are detected in about 1 in 1,000 infants and are the most common congenital heart defects (about 25%). Holes can develop anywhere in the muscular interventricular (IV) septum, but the most common VSDs occur in the upper membranous part of the septum. The embryonic basis is the failure of the spiral septum to properly fuse with the IV septum and endocardial cushions. Blood is diverted from the right ventricle to the left through the VSD as the systemic blood pressure increases relative to the pulmonary with growth of the infant and maturation of the airway. The lungs and left side of the heart get too much blood, and congestive heart failure and pulmonary edema can result.

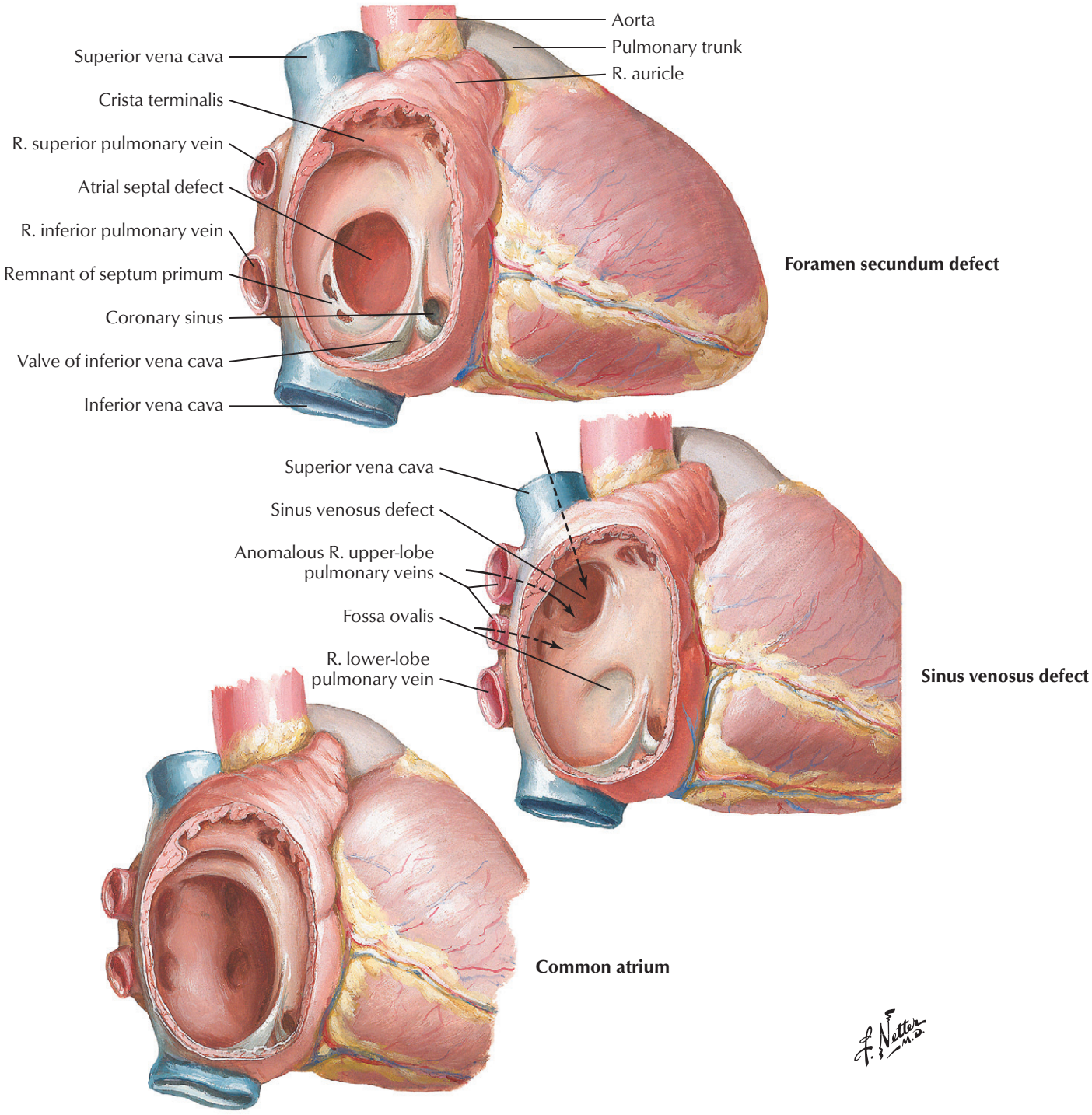


FIGURE 4.25 ATRIAL SEPTAL DEFECTS

Atrial septal defects (ASDs) usually occur when the foramen ovale or foramen secundum is too large, resulting in overlap with one another. A very small opening of this type is a "probe patent" foramen ovale found in 25% of the population. It is of no consequence. Other ASDs result when the septum primum fails to fuse with the endocardial cushions, when the sinus venosus is not properly incorporated into the right atrium, or when perforations develop anywhere in the interatrial septum. With the low blood pressure in the atria, most ASDs are not clinically significant unless there are other heart defects that cause a shunting of blood between the atria.

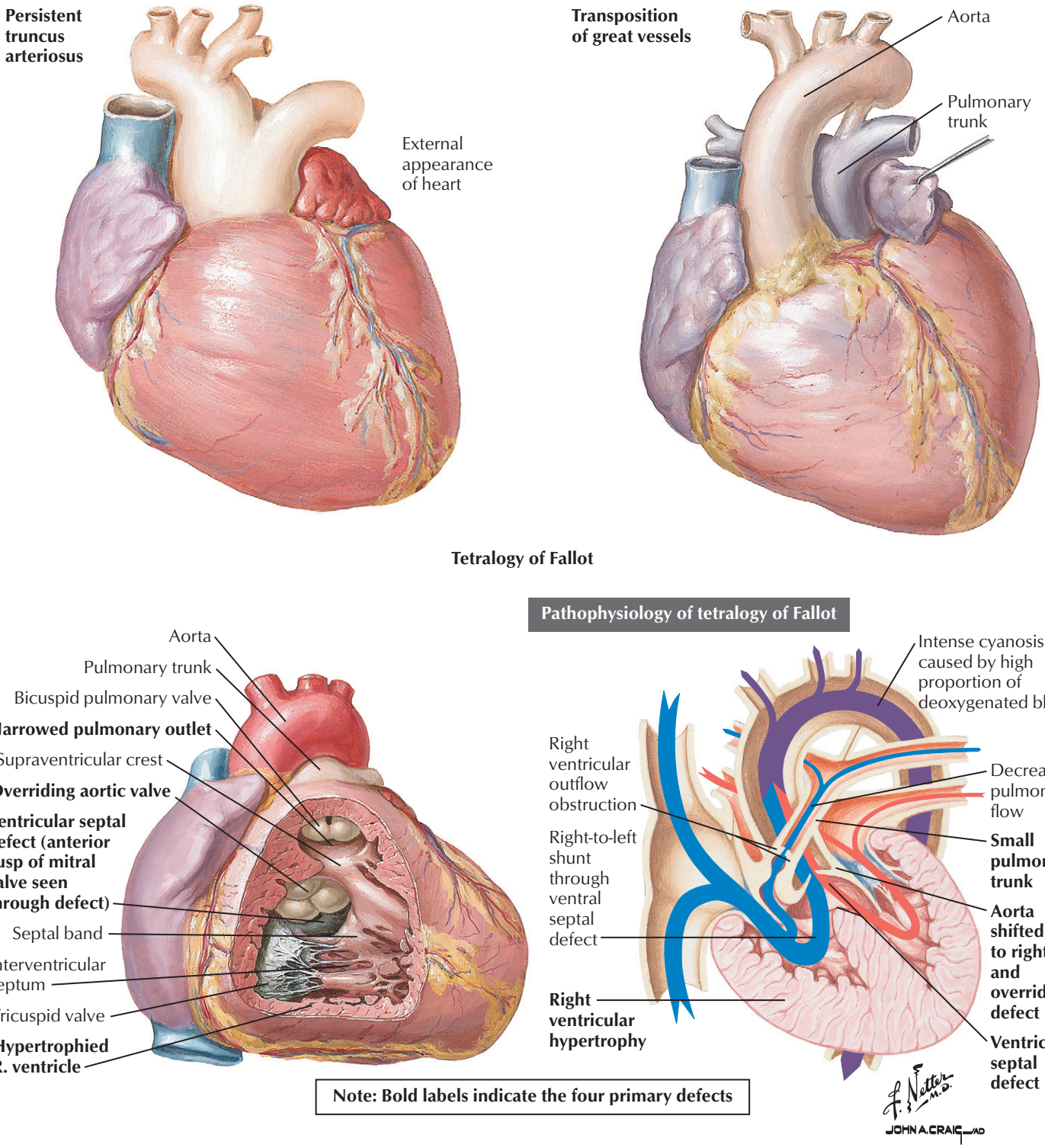


FIGURE 4.26 SPIRAL SEPTUM DEFECTS

The spiral septum may not develop (persistent truncus arteriosus), may not take a spiral course (transposition of the great vessels), or may divide the truncus arteriosus unequally leading to the four primary defects shown above in tetralogy of Fallot. Any communication between the ascending aorta and pulmonary trunk has a physiological result similar to ventricular septal defect (VSD)—blood is diverted from the systemic to the lower-pressure pulmonary circulation. Transposition results in death at birth unless there is mixing of blood between the two systems (e.g., through a VSD). A patent ductus arteriosus is often present in tetralogy of Fallot. If it is large, it is a significant route for blood to get to the lungs from the systemic circulation in the aortic arch.

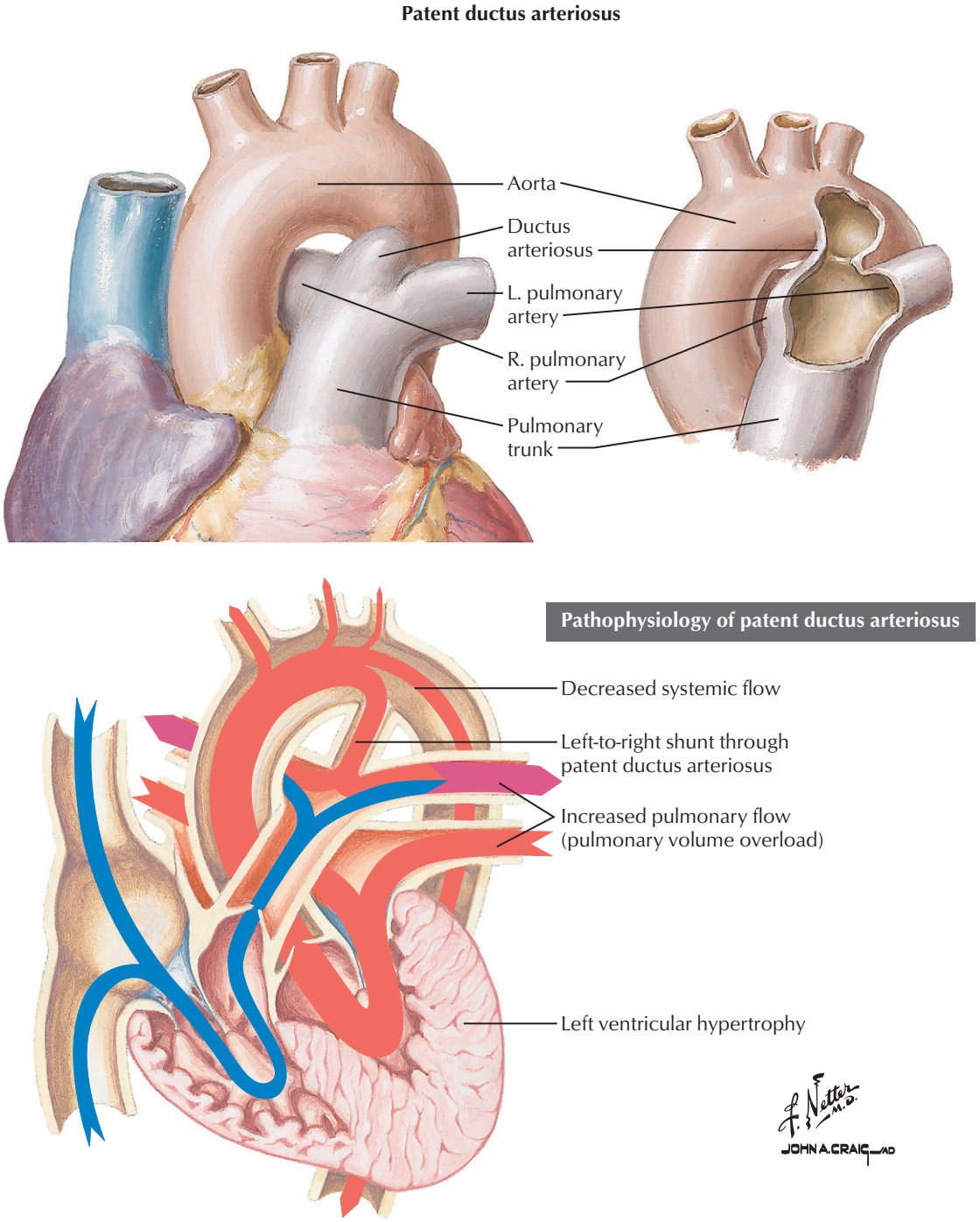


FIGURE 4.27 PATENT DUCTUS ARTERIOSUS

Large, patent ductus arteriosus results in pulmonary overload if it persists. Any communication between the left and right outflow tracts is subject to the pressure differential that develops as the pulmonary blood pressure becomes lower relative to the systemic pressure. A normal-sized ductus arteriosus remains patent for 2 weeks after birth. Although pulmonary vascular resistance begins to fall during this time, it is possible for blood to be diverted from the pulmonary trunk into the aorta if intrapleural pressure rises. This accounts for cyanosis in infants with prolonged crying spells.

Terminology

Angiogenesis	Blood vessel development.
Aortic arch arteries	Arteries within the pharyngeal (branchial) arches flanking the foregut that connect the aortic sac with the paired dorsal aortae and give rise to most of the arteries of the neck.
Aortic sac	Arterial chamber at the distal end of the outflow tract of the primitive heart tube ventral to the foregut. It directs blood from the truncus arteriosus into the aortic arch arteries.
Bulbus cordis	A chamber in the primitive heart tube that develops into the upper, smooth, outflow portion of each ventricle.
Cardinal veins	Cardinal, subcardinal, and supracardinal veins are embryonic systems of veins that develop in temporal sequence and form most of the major somatic, renal, and gonadal veins.
Cardiac jelly	A gelatinous connective tissue layer between the endothelial heart tube and the myocardial mantle layer. Its significance is unknown.
Cardiogenic mesoderm	Mesoderm from the primitive streak that migrates around the oropharyngeal (oral) membrane to midline position at the cranial end of the embryo. It is continuous with the lateral plate mesoderm on either side. All structures of the heart and pericardial sac develop from cardiogenic mesoderm.
Coarctation	An abnormal constriction.
Cyanosis	(G., "blue") Bluish coloration of the skin and mucous membranes from lower oxygen levels in the blood.
Ductus arteriosus	A lung shunt connecting the pulmonary trunk to the arch of the aorta. After birth it remains patent for a few weeks before forming the fibrous ligamentum arteriosum.
Ductus venosus	Liver bypass shunting blood from the umbilical vein into the inferior vena cava. It becomes the ligamentum venosum.
Endocardial cushions	Dorsal and ventral (or superior/inferior) partitions of the heart tube that fuse to first separate blood flow into left and right sides.
Epicardium	Visceral pericardium on the surface of the heart. Cells from the cardiogenic mesoderm on the sinus venosus migrate over the myocardial mantle layer to form the epicardium.
Foramen ovale	A lung shunt where blood passes from the right atrium to the left atrium. In common usage it refers to the entire atrial bypass that includes the foramen secundum.
Sinus venosus	The first part of the venous end of the heat tube receiving blood from the umbilical vein, common cardinal veins, and vitelline veins.
Stenosis	(G., "narrowing") The narrowing of a vessel, duct, or canal.
Tetralogy of Fallot	"Four" secondary heart defects resulting from a primary spiral septum defect that divides the truncus arteriosus unequally: (1) pulmonary stenosis, (2) ventricular septal defect, (3) aorta overriding and draining both ventricles, and (4) right ventricular hypertrophy.
Transverse sinus	The space between the great arteries and the superior vena cava occupied by the mesentery of the heart. The heart tube sinks into the pericardial coelom and becomes suspended by a mesentery, the dorsal mesocardium. As the arterial and venous ends of the heart tube approach each other, the mesocardium breaks down to form the transverse sinus.
Vitelline vessels	Circulation to the yolk sac, which is the first source of blood cell production. The proximal, intraembryonic portions persist as the major midgut and hindgut arteries, liver veins, and hepatic portal system.

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CHAPTER 5

THE RESPIRATORY SYSTEM

PRIMORDIA FOR THE UPPER AIRWAY

Nasal sac (from nasal placode), stomodeum, and foregut.

PRIMORDIA FOR THE LOWER AIRWAY

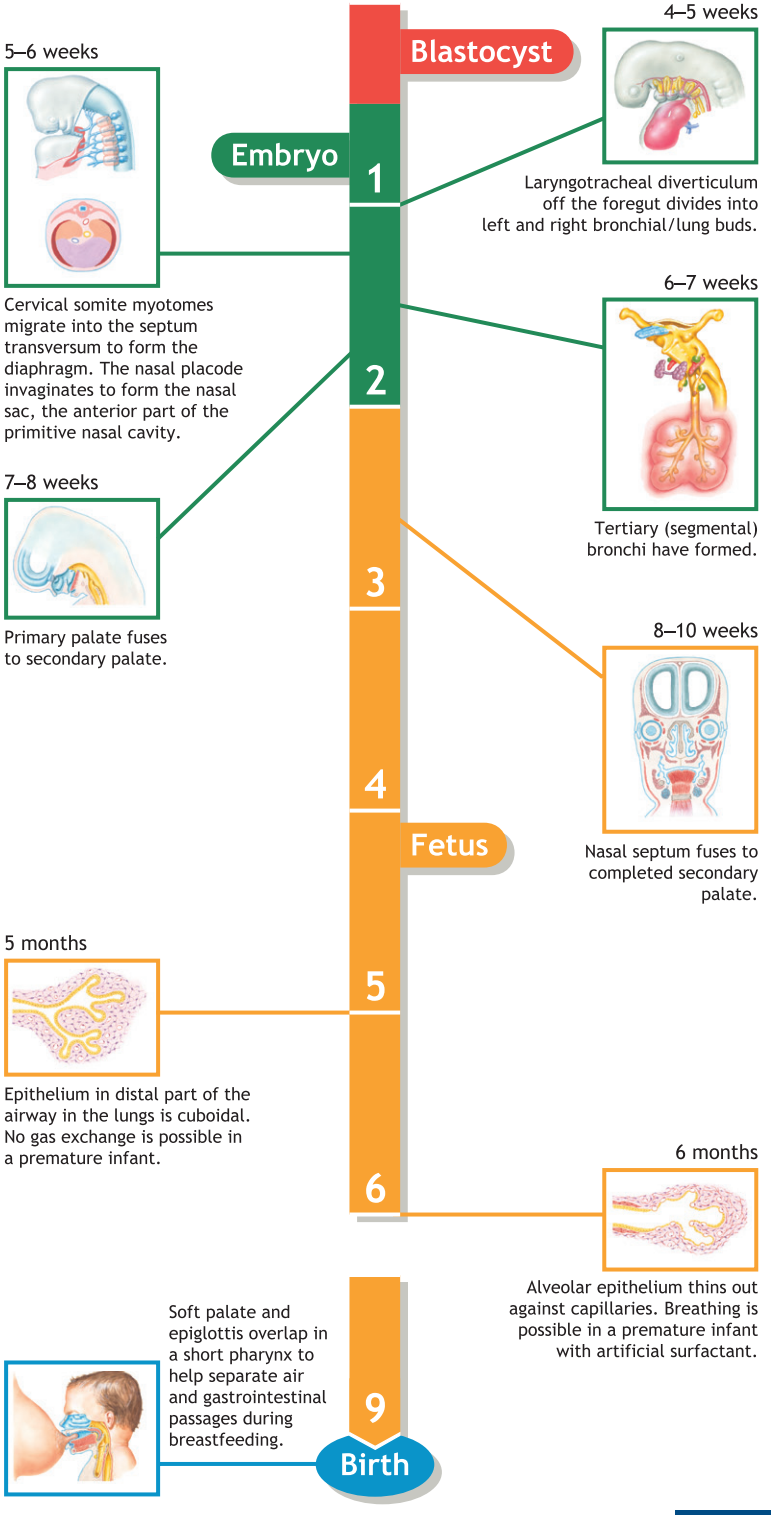
Laryngotracheal diverticulum (lung bud) of foregut splanchnopleure.

PLAN

The main developmental event in the upper airway is the division of the stomodeum by the palate into separate respiratory (nasal) and gastrointestinal (oral) components so that respiration can occur during mastication. The development of the lower airway is characterized by the creation of the pleural cavity and the extensive branching of the airway within it. The continuous intraembryonic coelom is partitioned into separate pleural, pericardial, and peritoneal components, each lined by mesothelium. A bud from the laryngotracheal diverticulum pushes into each pleural sac and continues to branch for more than 22 generations to produce a surface area of 85 m^2 for gas exchange between alveoli and the bloodstream.

TIMELINE

Prenatal Time Scale (Months)



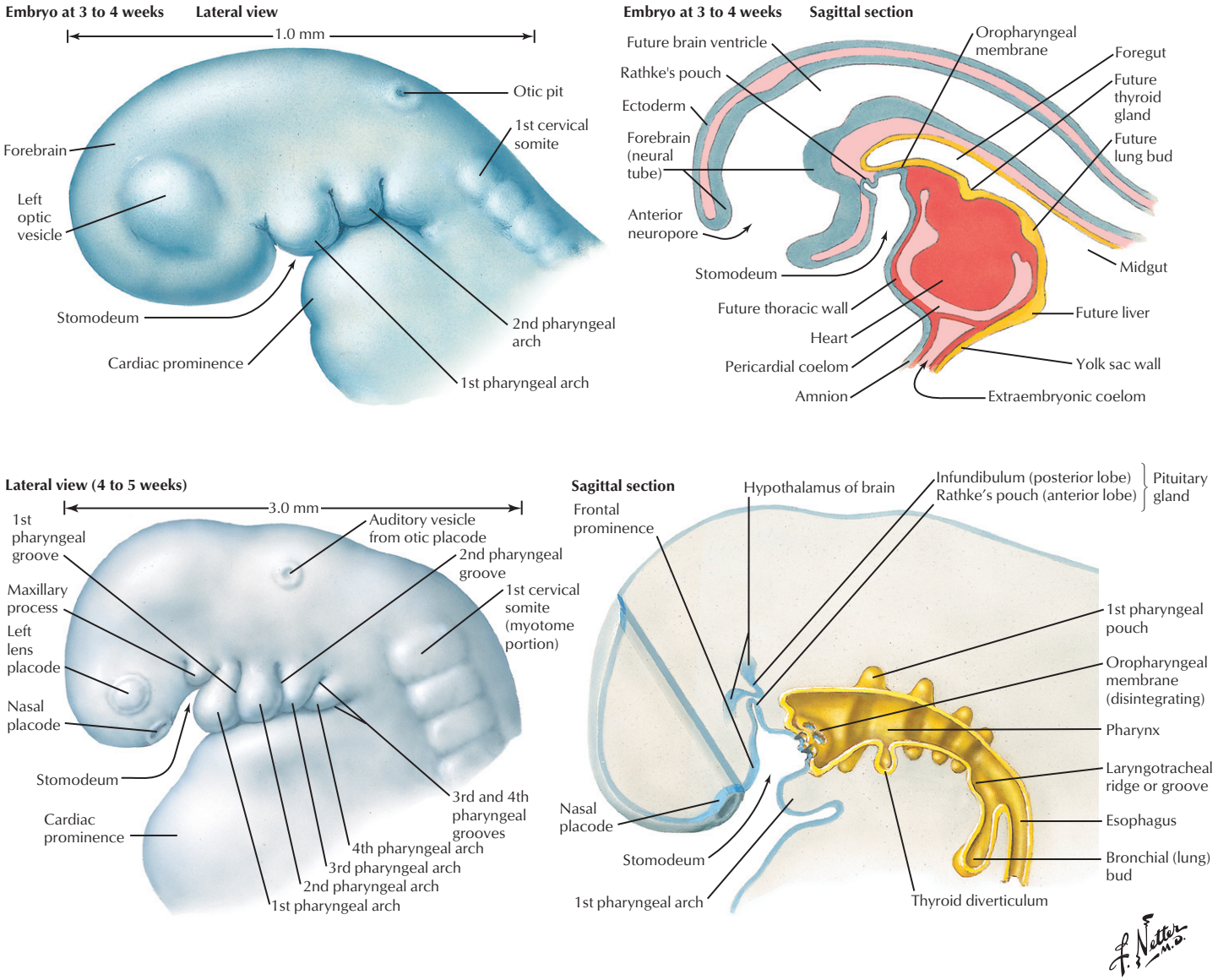
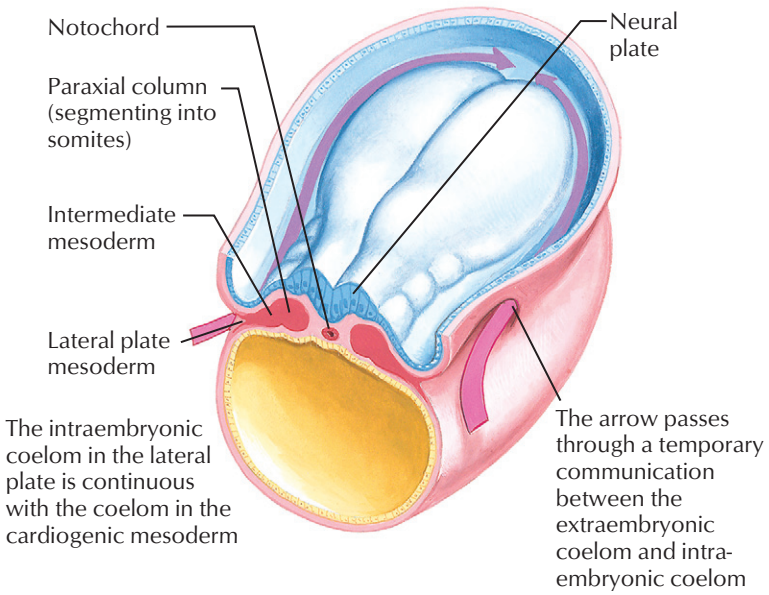


FIGURE 5.1 EARLY PRIMORDIA

The early primordia of the upper and lower airways:

- Stomodeum
- Nasal placode
- Foregut
- Laryngotracheal diverticulum (lung bud)
- Septum transversum
- Intraembryonic coelom

A. Cross section of embryo



B. Sagittal section at 5 to 6 weeks

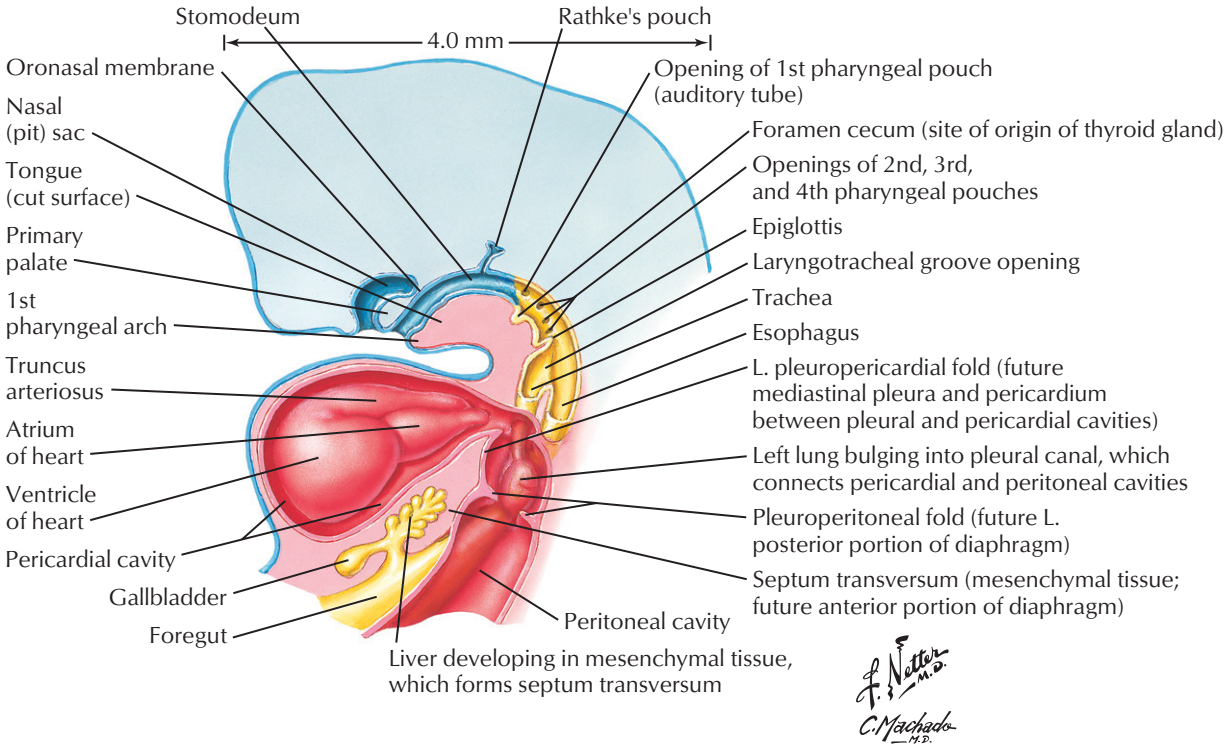


FIGURE 5.2 FORMATION OF THE PLEURAL CAVITIES

The **intraembryonic coelom** begins as cavities form in the lateral plate mesoderm on each side and in the midline cardiogenic mesoderm. Shown in part B is the interior of the coelom on the left extending from the abdominal region through the left pleural canal into the pericardial cavity. From there it continues under the heart and back down the other side of the midline gastrointestinal tract and its supporting dorsal and ventral mesenteries. The U-shaped coelomic tube is partitioned into separate peritoneal, pleural, and pericardial cavities by **pleuroperitoneal membranes** and pleuropericardial folds, where the common cardinal veins (not shown) pinch the coelom to separate the pleural cavity from the pericardial cavity.

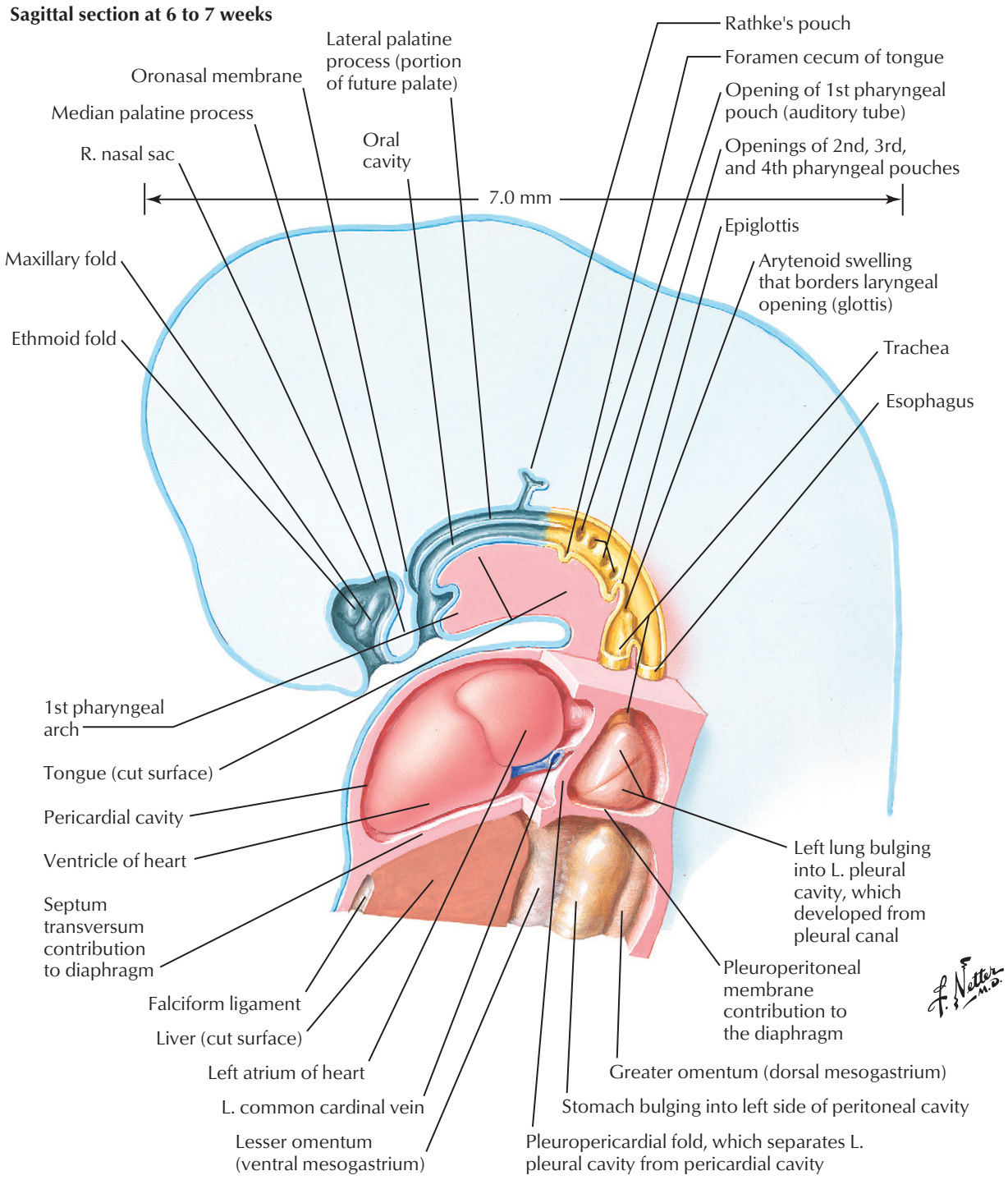


FIGURE 5.3 THE RELATIONSHIP BETWEEN LUNGS AND PLEURAL CAVITIES

The **septum transversum** and **pleuroperitoneal membranes** of the developing diaphragm separate the peritoneal cavity from the pleural and pericardial cavities in the thorax. The pleural and pericardial cavities are also separate from each other. The mesenchyme lining the three cavities differentiates into the simple squamous epithelium **(mesothelium)** of pleura, peritoneum, and pericardium. The lungs grow into the pleural sac of mesothelium much like a fist pushing into a balloon. The mesothelium on the surface of the lung is **visceral pleura. Parietal pleura** lines the thoracic wall, diaphragm, and mediastinum.

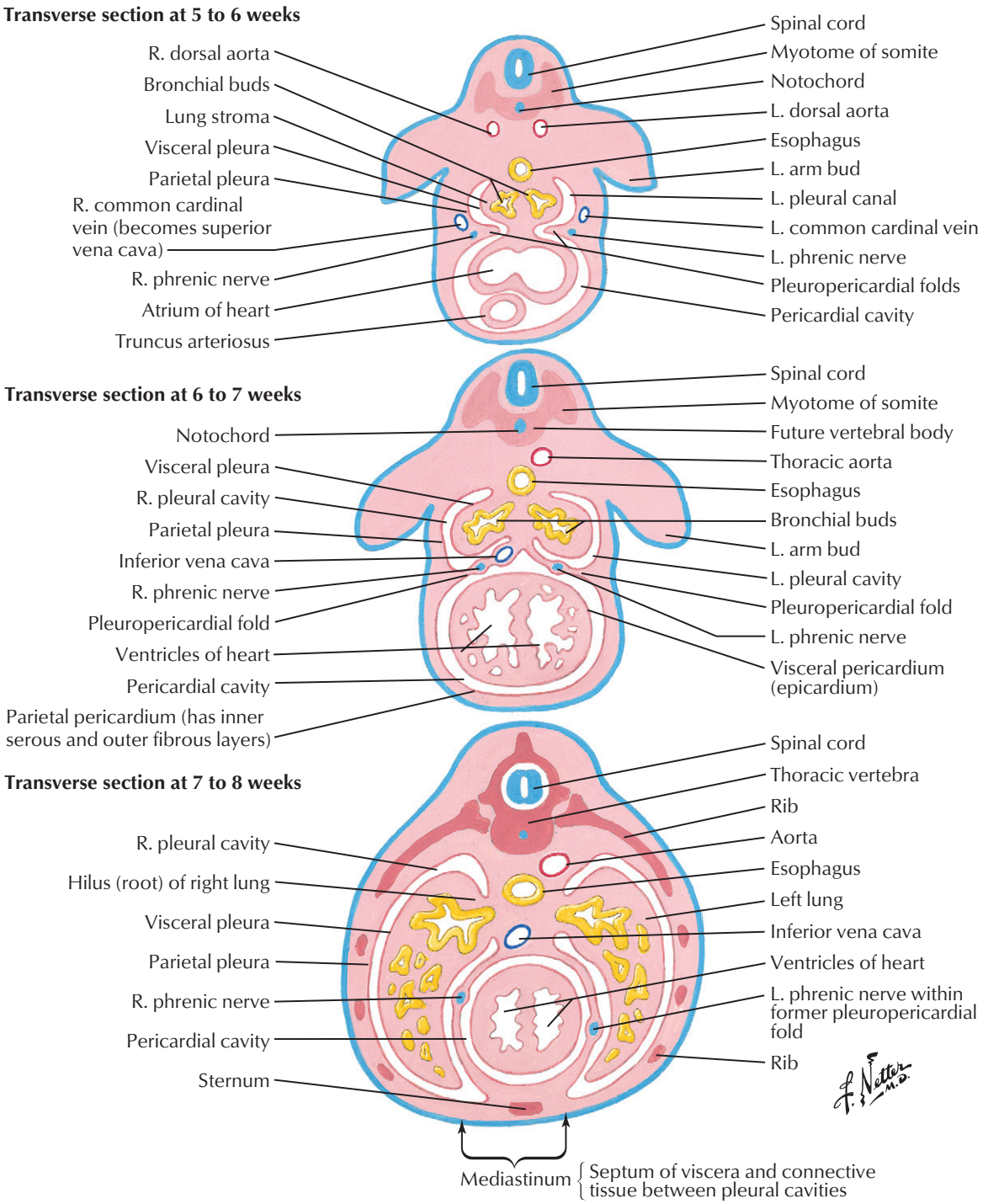


FIGURE 5.4 VISCERAL AND PARIETAL PLEURA

The division of pleural and pericardial cavities is complete by 7 weeks. Visceral and parietal pleura are continuous with each other at the root of the lung. Visceral and parietal pericardia are continuous around the great vessels at the top of the heart (not shown). As the lungs enlarge, the pleural cavity becomes a potential space with a little serous fluid to reduce friction as visceral and parietal pleura slide against each other during respiration.

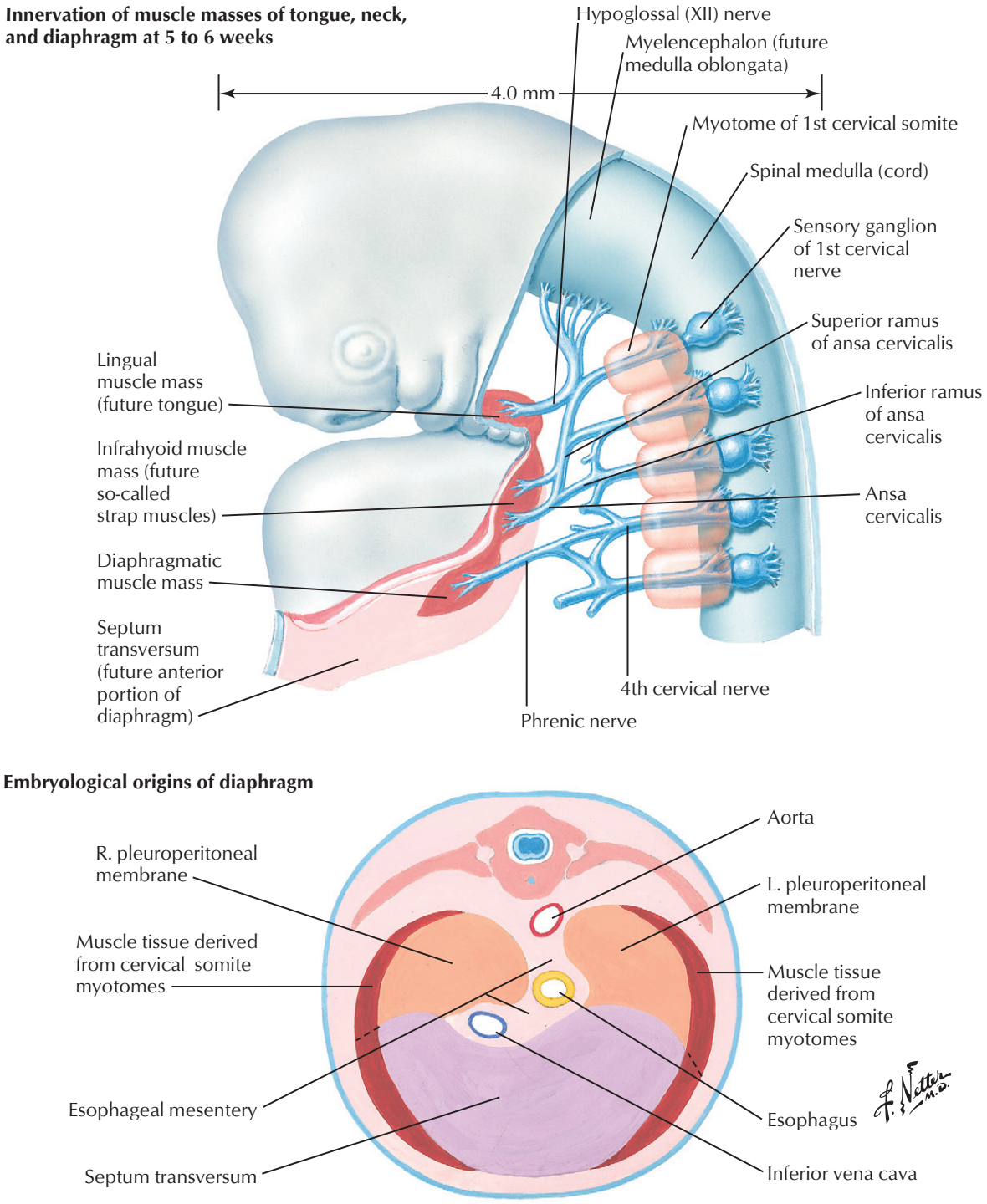


FIGURE 5.5 DEVELOPMENT OF THE DIAPHRAGM

The diaphragm develops from four primordia:
Septum transversum, a mesenchyme partition between the embryonic thorax and abdomen
Pleuroperitoneal membranes
Mesentery of the esophagus
Cervical somite myotomes (for muscle cells of the diaphragm)

The septum transversum develops adjacent to the cervical region; it then "descends" relative to the growth of the embryonic trunk. It carries with it the **phrenic nerve,** the ventral ramus of spinal nerve segments C3, C4, and C5.

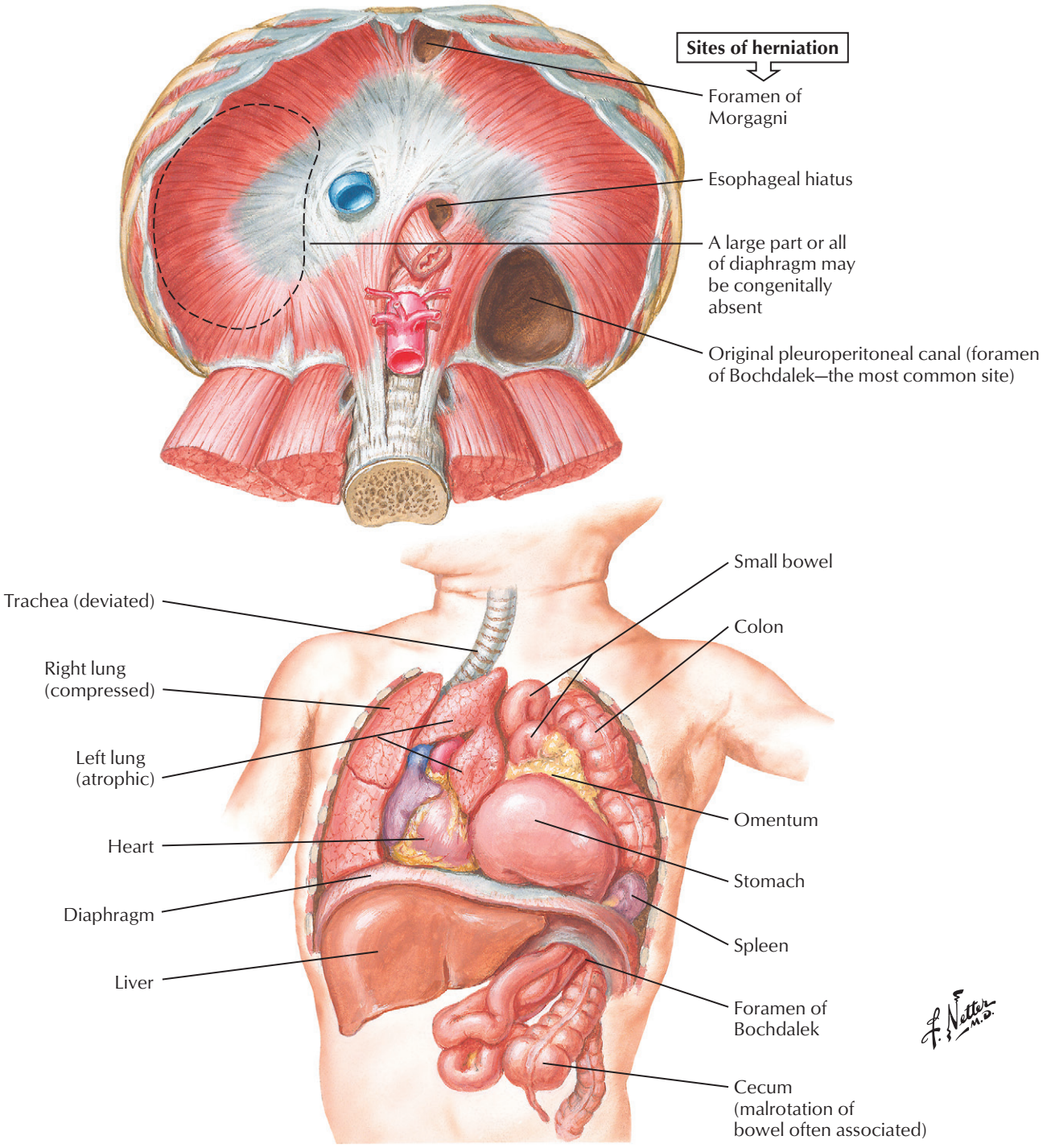


FIGURE 5.6 CONGENITAL DIAPHRAGMATIC HERNIA

This is the most common diaphragmatic hernia. It results from a failure of the pleuroperitoneal membranes to grow across the intraembryonic coelom (foramen of Bochdalek). Abdominal organs may extend into the thoracic cavity, resulting in an abnormally distended thorax and flat stomach region. Other diaphragmatic hernias are septum transversum defects or result from natural openings that are unusually large.

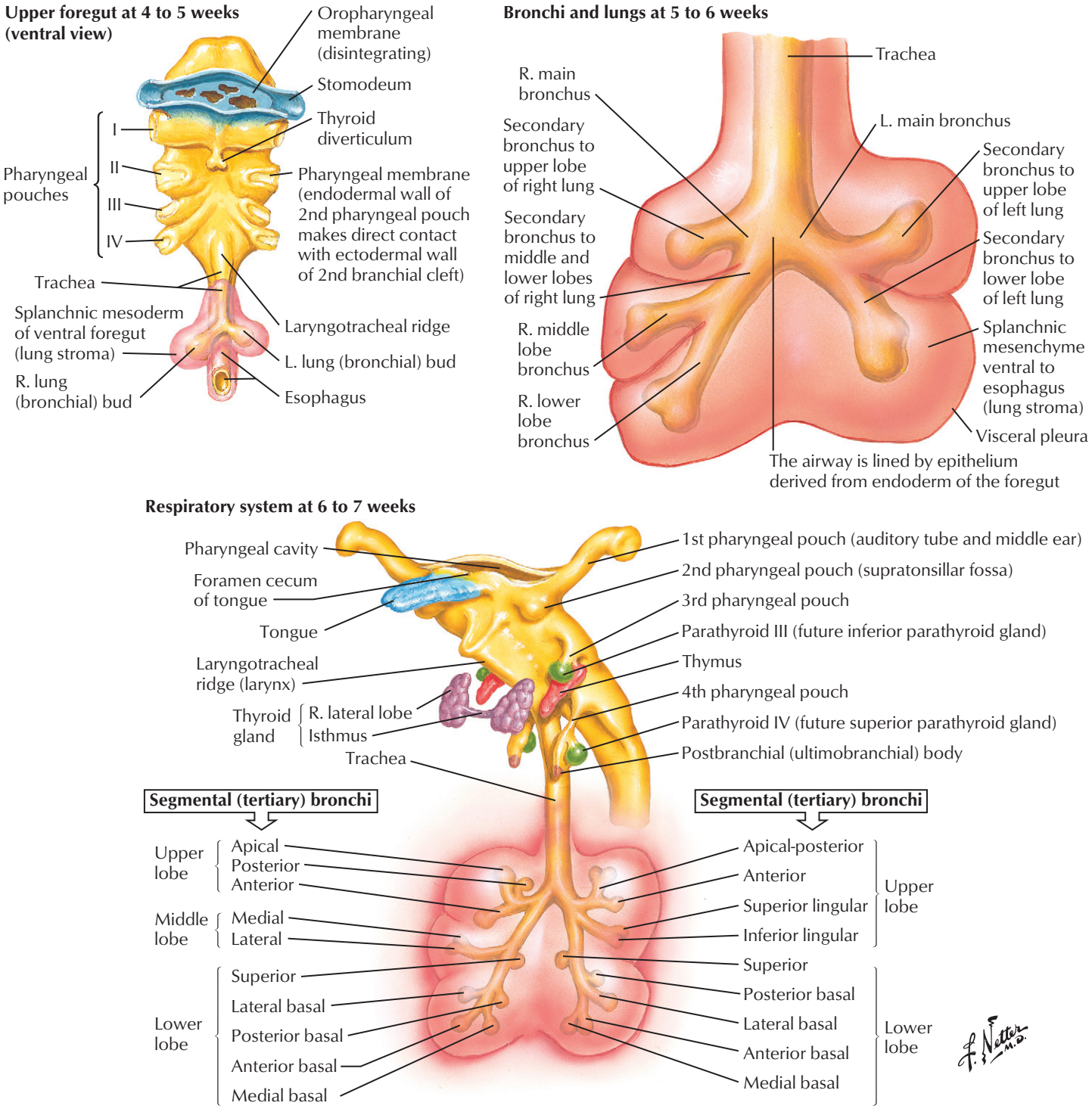


FIGURE 5.7 THE AIRWAY AT 4 TO 7 WEEKS

The **laryngotracheal diverticulum** grows ventrally off the foregut and begins an extensive series of branching in the fourth week. It is composed of splanchnopleure, with the endoderm forming the epithelial **parenchyma** of the future airway and the mesoderm forming the connective tissue **stroma.** The diverticulum first branches into a left and right lung bud with **primary bronchi.** The next division forms the lobes of the lung with their **secondary (lobar) bronchi.** Secondary bronchi divide into **tertiary (segmental)** bronchi that supply the **bronchopulmonary segments** of the lungs.

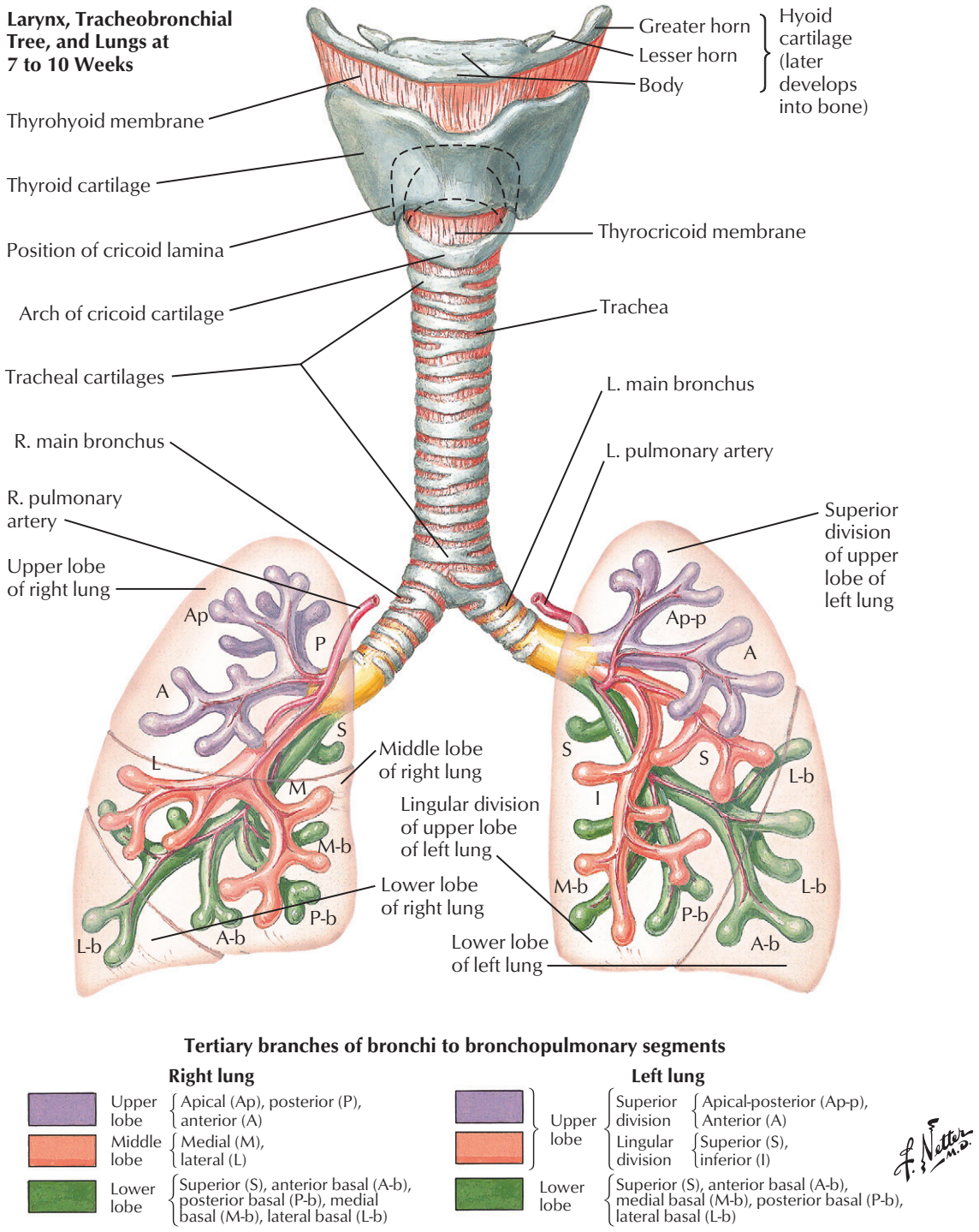


FIGURE 5.8 THE AIRWAY AT 7 TO 10 WEEKS

By 10 weeks, the cartilages of the larynx and cartilage rings of the trachea and larger bronchi have formed. The bronchi continue their generations of branching. There are 10 bronchopulmonary segments in the right lung and 9 in the left. The left lung has only two lobes (and two secondary bronchi) instead of three. The lingula of the left lung is equivalent to the middle lobe of the right. The pulmonary arteries branch with the bronchi, while the veins run between the segments.

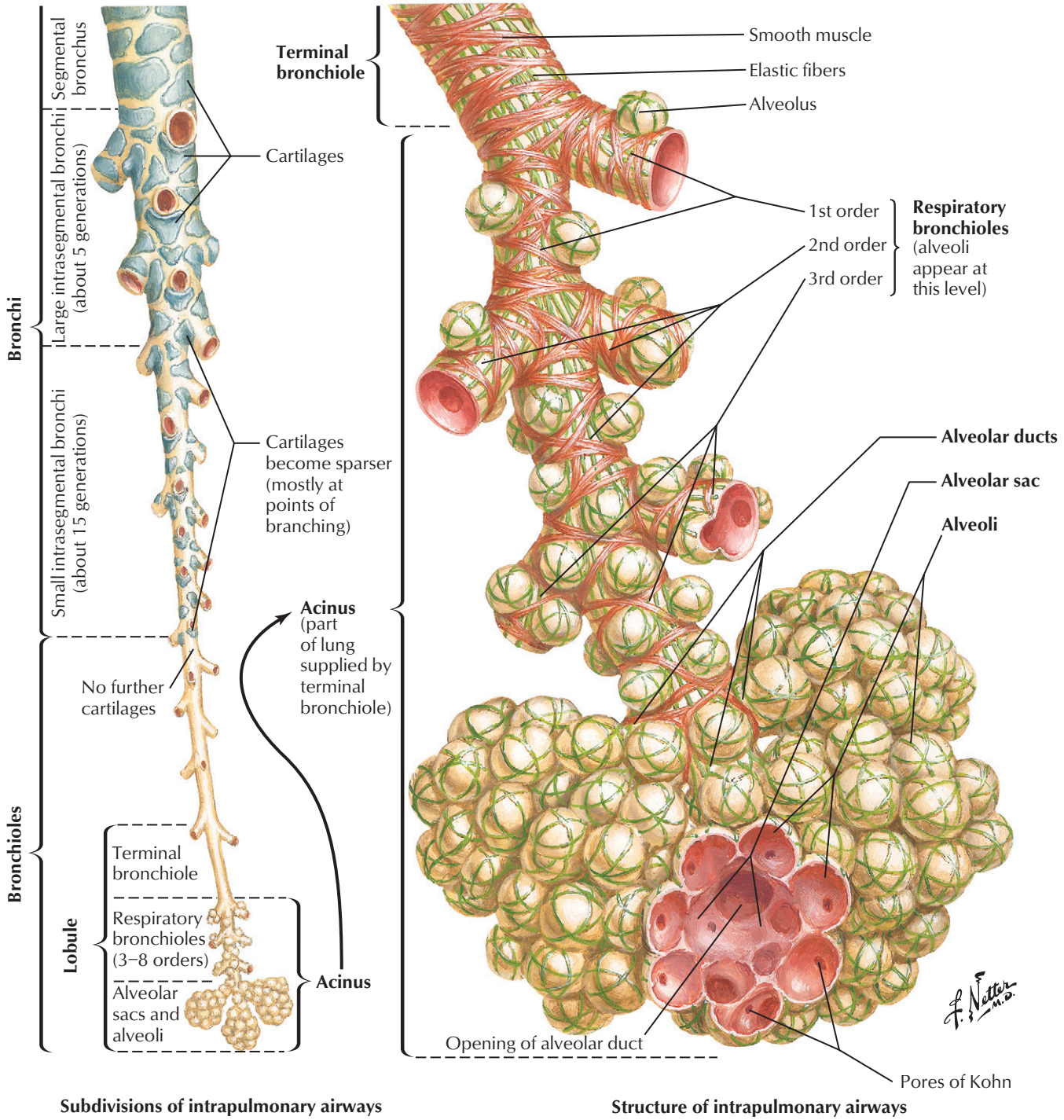


FIGURE 5.9 DEVELOPMENT OF BRONCHIOLES AND ALVEOLI

The tertiary bronchi continue to divide for many generations; the total ranges from 23 to 301, depending on the region of the lung. Bronchi become bronchioles when hyaline cartilage is no longer present in the walls. The bronchial tree eventually terminates in **alveoli,** the saclike structures where gas exchange occurs.

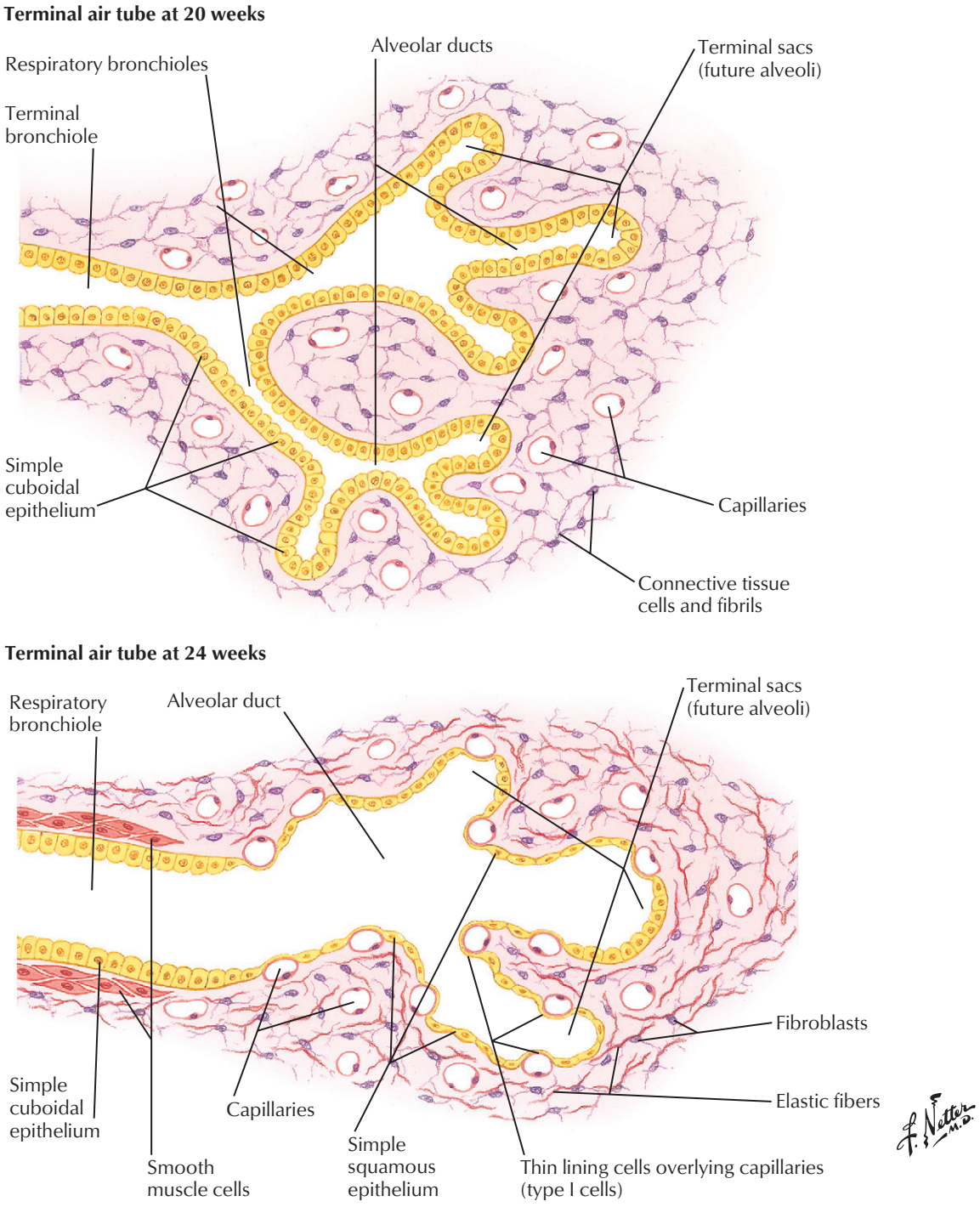


FIGURE 5.10 BRONCHIAL EPITHELIUM MATURATION

The trachea and larger bronchi are lined by **pseudostratified columnar (respiratory) epithelium** with cilia and mucus-producing goblet cells. The epithelium becomes simple cuboidal in the smaller bronchi and simple squamous in mature alveoli. At 20 weeks, all epithelium is simple cuboidal in the distal airway and not closely applied to the capillaries. No gas exchange is possible in a premature infant of this age. At 6 months, the future alveoli are mature enough for gas exchange, but the type II alveolar cells are not yet producing surfactant, which reduces surface tension to prevent alveoli from collapsing. Life can be sustained only with artificial surfactant or by maintaining positive pressure in the alveoli.

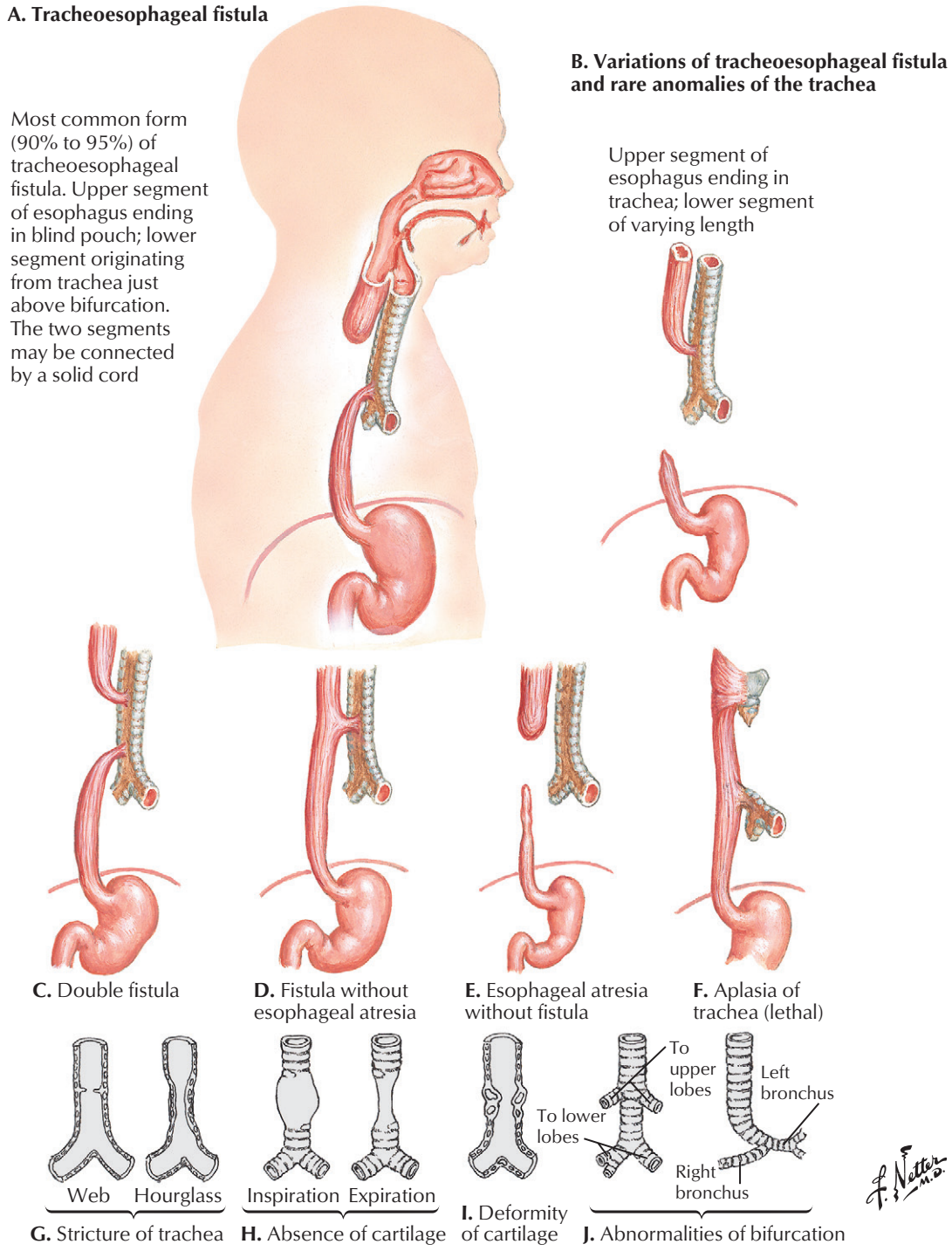


FIGURE 5.11 CONGENITAL ANOMALIES OF THE LOWER AIRWAY

The laryngotracheal diverticulum is closely applied to the ventral surface of the developing esophagus. The lumen of the esophagus closes from the proliferation of epithelial cells and then reopens. Disruption of this process can result in **tracheoesophageal fistula** (i.e., abnormal communication between the trachea and esophagus). A variety of possibilities plus some other types of anomalies of the trachea are illustrated.

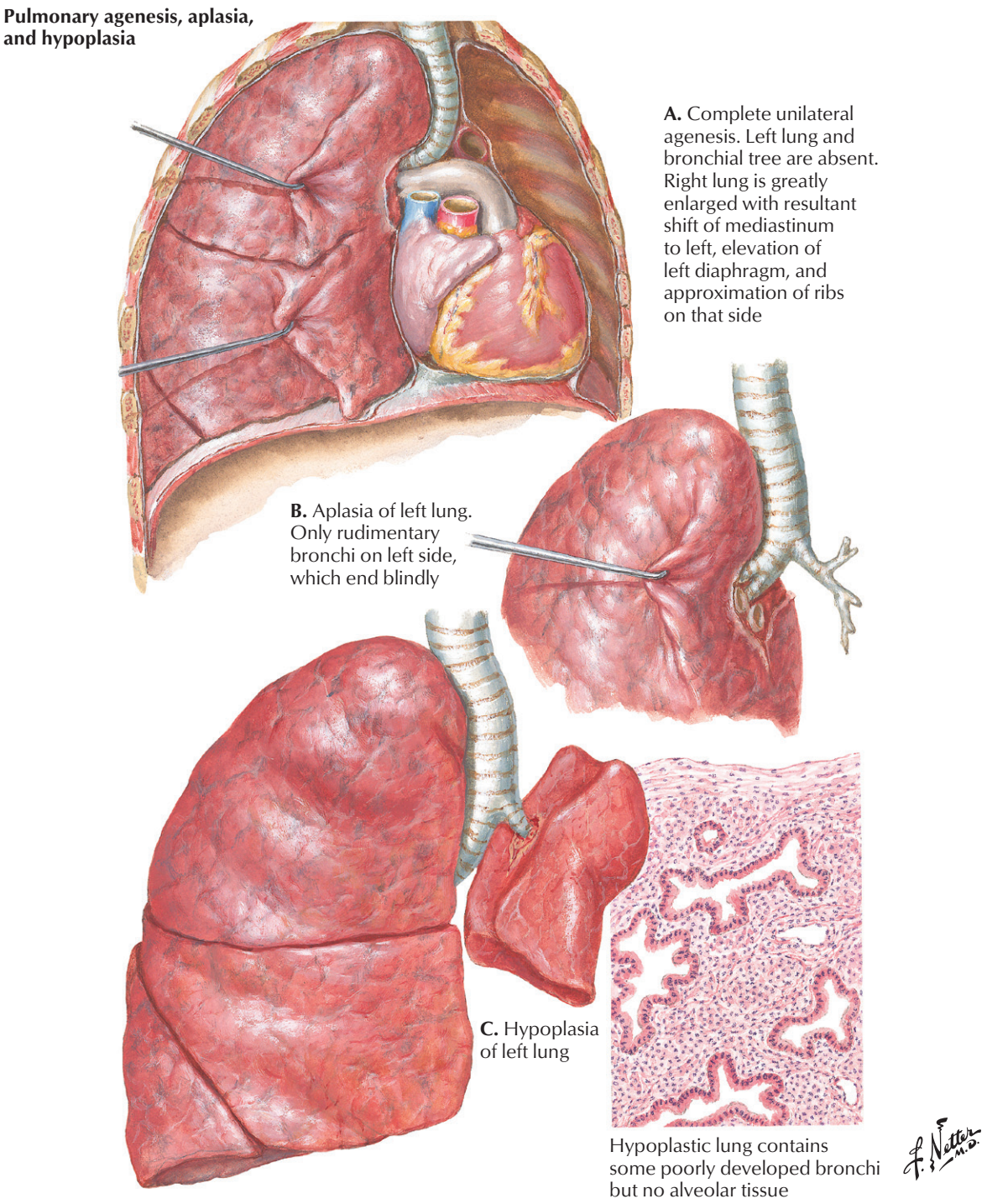


FIGURE 5.12 AIRWAY BRANCHING ANOMALIES

Like any organ or gland that develops by the sequential branching of its primordium, there are numerous possibilities for asymmetry (and other branching abnormalities as seen in part J in Figure 5.11). Shown here is the result of the lack of a left lung bud or a small left bronchial bud with and without lung tissue.

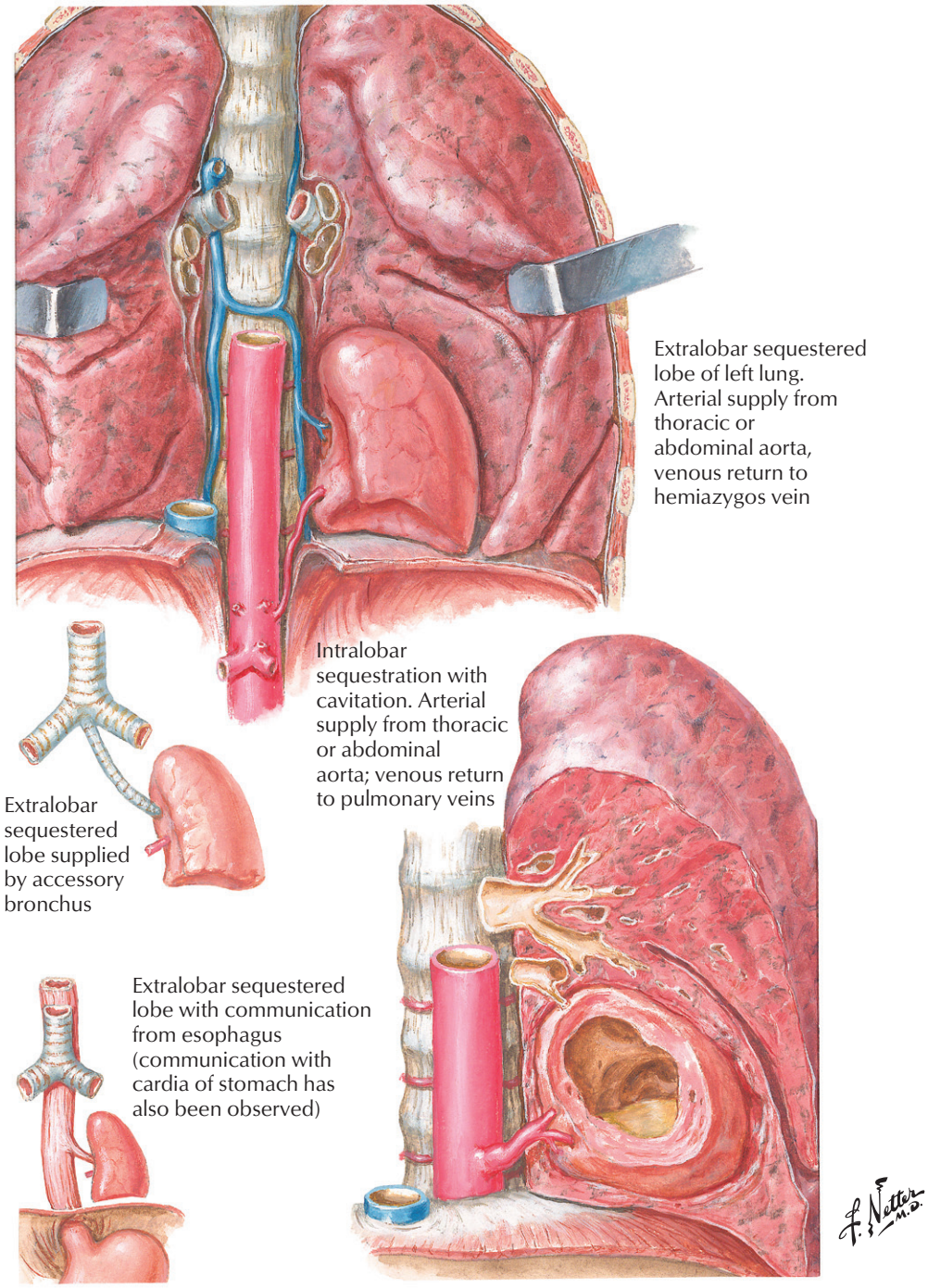


FIGURE 5.13 BRONCHOPULMONARY SEQUESTRATION

More complicated than branching asymmetry is **sequestration,** the separation of a small, extra lobe of lung tissue from the normal bronchial tree. It may be inside or outside the lung, but it is typically supplied by the systemic circulation rather than by the pulmonary. It may have abnormal communications with intralobar bronchi or develop from an extra bud off the laryngotracheal diverticulum or even other components of the foregut (e.g., esophagus or stomach).

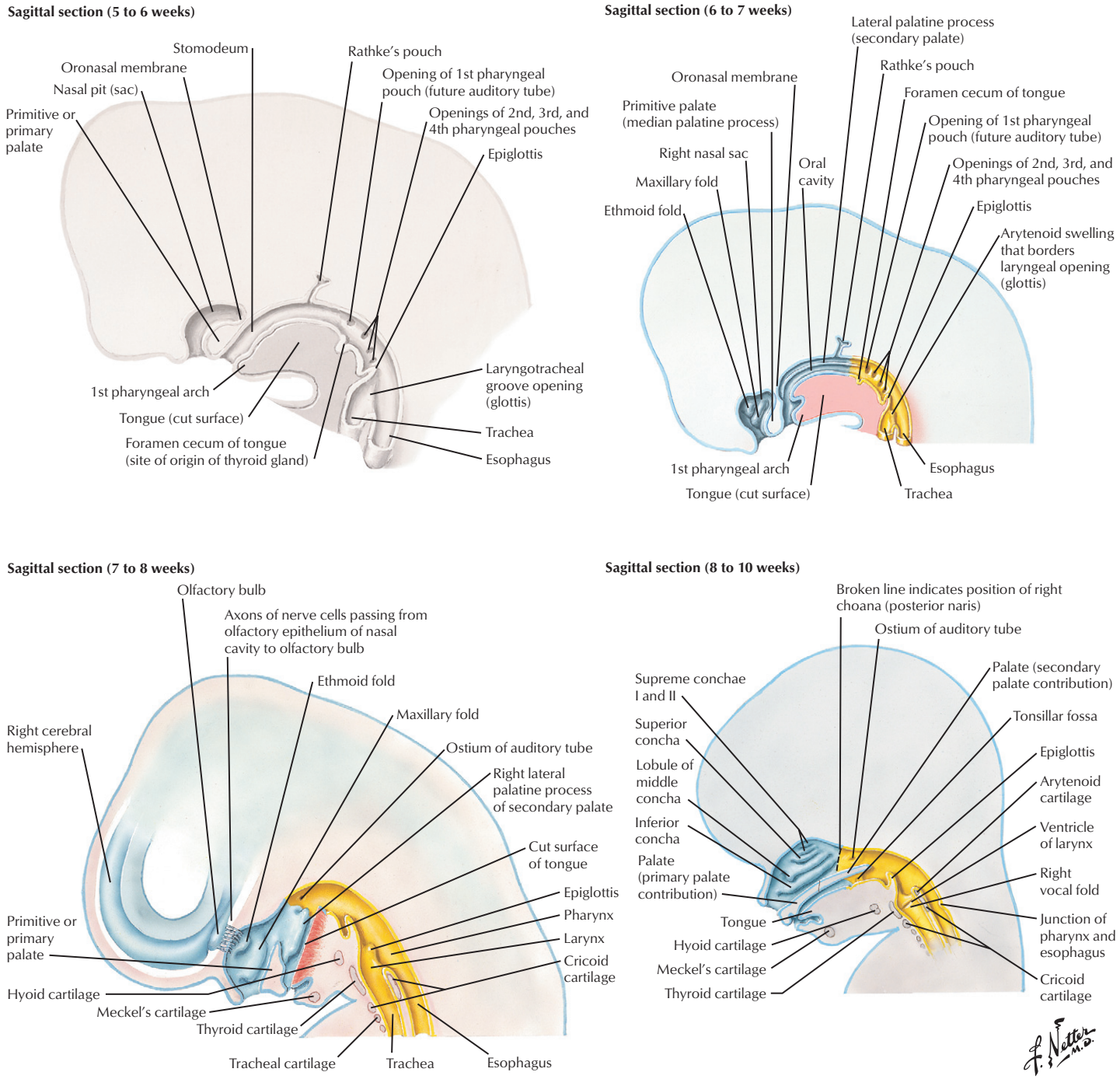


FIGURE 5.14 PALATE FORMATION IN THE UPPER AIRWAY

The upper airway develops from the **foregut,** the upper half of the **stomodeum,** and the **nasal sacs,** which are invaginations of the ectodermal nasal placodes. Lateral palatine processes grow toward the midline to divide the stomodeum into nasal and oral components. The nasal sacs break through to the airway part of the stomodeum, above the lateral palatine processes. The tissue between the nasal sacs and stomodeum is the primary palate, and the lateral palatine processes form the secondary palate. Palate formation is completed when the primary palate, lateral palatine processes of the secondary palate, and the nasal septum all fuse to each other. See Chapter 9 for more details.

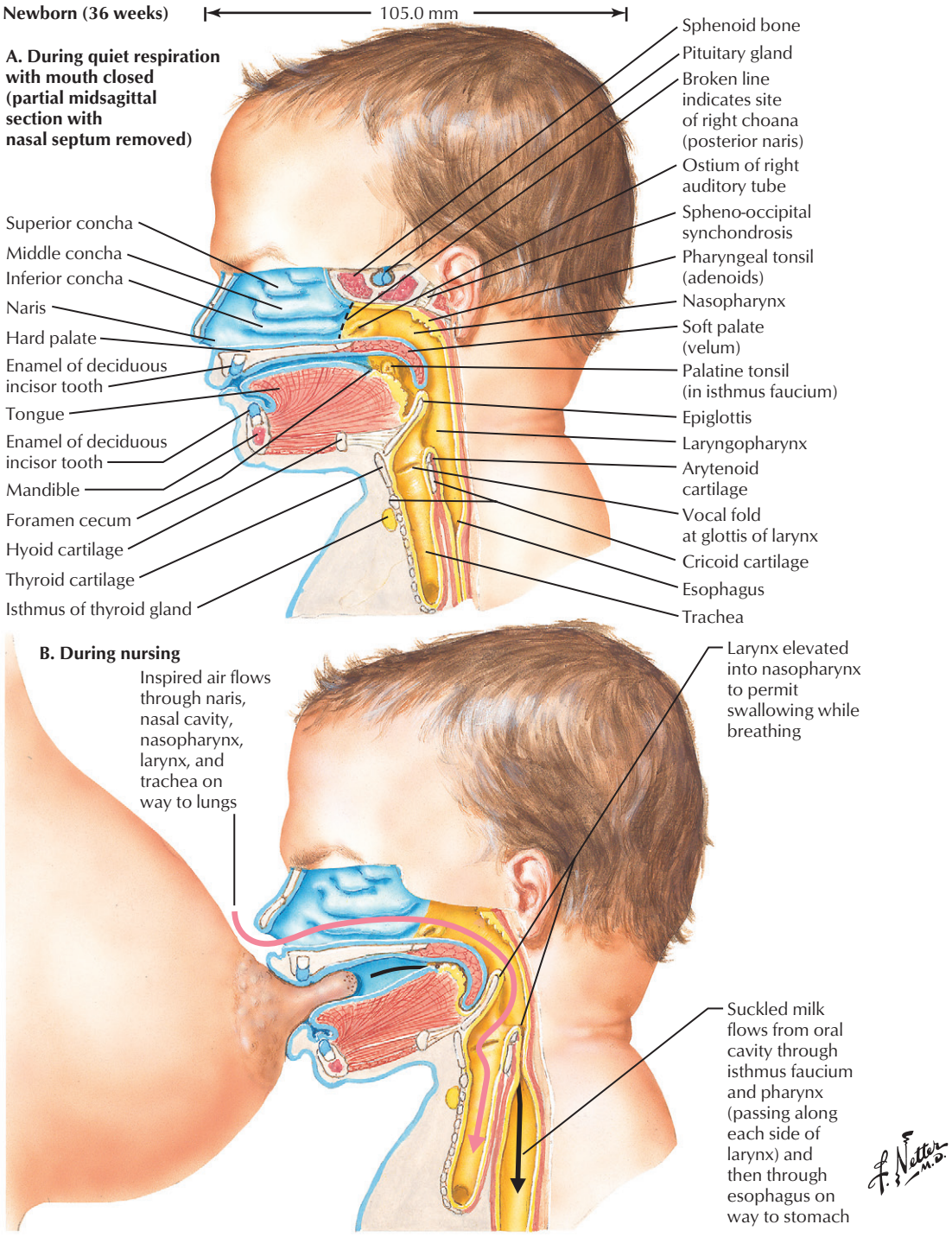


FIGURE 5.15 THE NEWBORN UPPER AIRWAY

The airway and gastrointestinal tract are more separated in newborns than in adults. The pharynx is short, and the soft palate and epiglottis of the larynx overlap each other during breastfeeding. Air passes from the nasal cavity more directly into the larynx and lower airway. Food is diverted around each side of the soft palate and epiglottis as it passes into the esophagus. The pharynx is longer in adults, and the oropharynx is a common chamber for the passage of food and air.

Terminology

Alveolus	(L., "hollow") Saclike terminal elements of the distal airway in the lungs, where gas exchange occurs between alveolar air and the bloodstream. They total 300 million.
Bronchopulmonary segments	Subdivisions of lung lobes aerated by tertiary (segmental) bronchi, the third generation of branching of the trachea.
Carina	Cartilaginous ridge at the internal bifurcation point of the trachea into the left and right primary bronchi.
Coelom	(Gr., "hollow") The pericardial, pleural, and peritoneal body cavities.
Epiglottis	Cartilaginous projection of the larynx into the laryngopharynx above the glottis.
Glottis	The aperture between the vocal folds (mucosa over the vocal "cords") in the larynx. It is the entryway into the lower airway.
Lobar bronchus	A bronchus supplying a lung lobe. The second generation of bronchial branching.
Lower airway	Larynx, trachea, and lungs (with the bronchial tree).
Main bronchus (right and left)	Mainstem bronchus that supplies an entire lung. It is the first order of branching of the trachea.
Mesothelium	The simple squamous epithelium that lines the body cavities. Mesothelia are pleura, peritoneum, and pericardium.
Pseudostratified ciliated columnar epithelium	Respiratory epithelium in the nasal cavities, most of the larynx, trachea, and larger bronchi. The nuclei appear to be stratified in section, but all of the cells touch the basal lamina.
Root of lung	All of the structures that enter and leave each lung—main bronchus, pulmonary artery and veins, bronchial arteries and veins, nerves, and lymphatics.
Segmental bronchus	A bronchus supplying a bronchopulmonary segment. The third (tertiary) generation of bronchial branching.
Septum transversum	Thick, transverse partition of mesenchyme in the embryo just caudal to the developing heart. It contributes to the diaphragm and stroma of the liver and gallbladder.
Serous fluid	Proteinaceous, watery fluid produced by the mesothelia lining the body cavities. It reduces friction between movements of parietal and visceral layers.
Surfactant	A fluid rich in phospholipids secreted by type II alveolar cells to reduce surface tension in the pulmonary alveoli. This prevents them from collapsing and contributes to the elastic properties of lung tissue.
Types I and II alveolar cells	Type I cells are the simple squamous cells forming most of the gas-exchanging walls of alveoli. Type II cells produce surfactant. They are equal in number to type I cells but occupy much less alveolar area because of their cuboidal shape.
Upper airway	Nasal cavity and pharynx.

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CHAPTER 6

THE GASTROINTESTINAL SYSTEM AND ABDOMINAL WALL

PRIMORDIUM

The foregut, midgut, and hindgut and their associated organs are derived from splanchnopleure (endoderm and splanchnic mesoderm of the lateral plate).

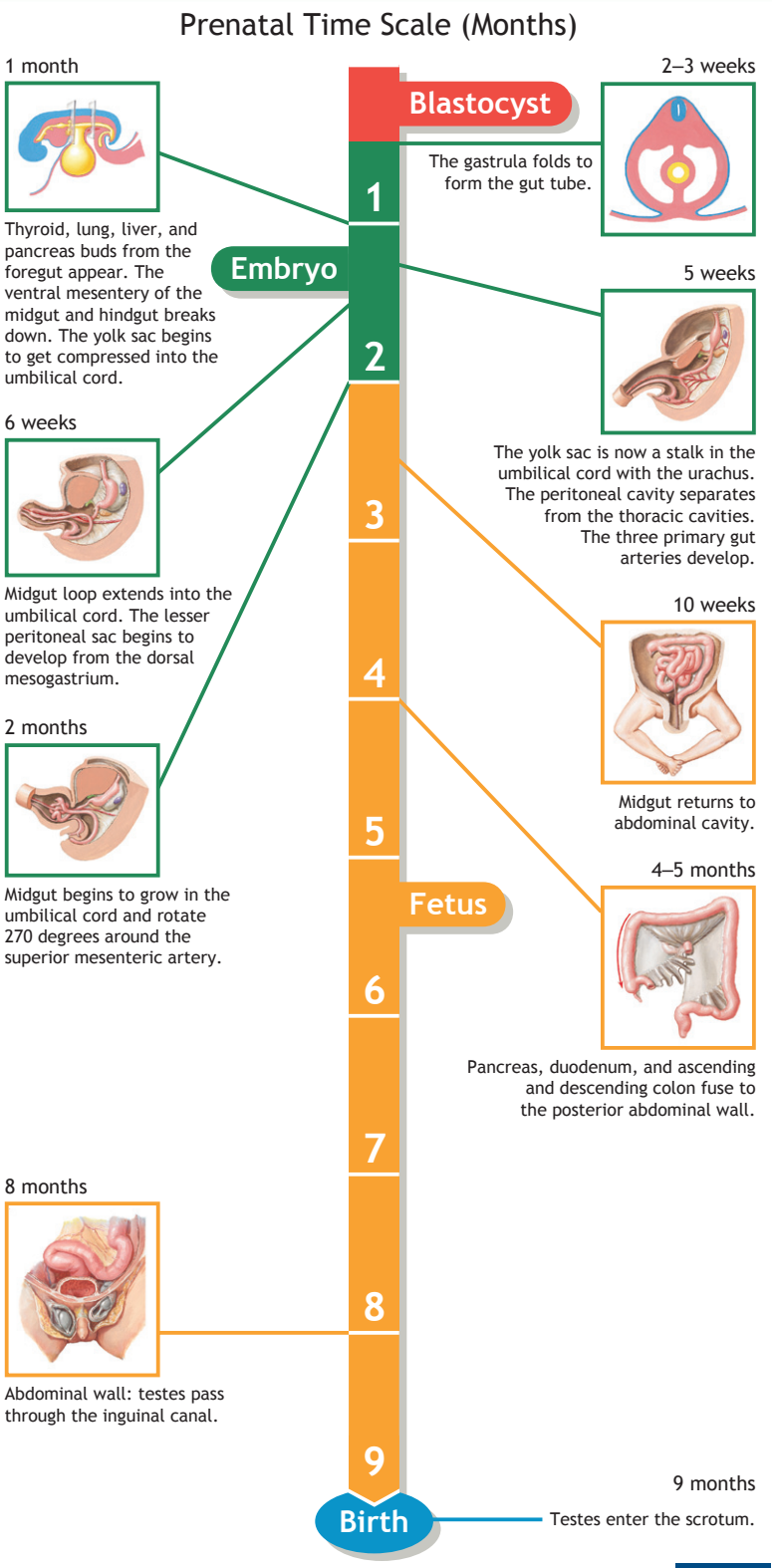
PLAN FOR THE GASTROINTESTINAL (GI) SYSTEM

Perhaps nowhere in the body is the organization of an organ system so simple in the embryo and its appearance so complex in the adult. The GI system in the abdomen first develops as a tube suspended by dorsal and ventral, sheetlike mesenteries. Blood vessels, autonomic nerves, lymphatic drainage, and mesentery structure are all organized according to abdominal foregut, midgut, and hindgut subdivisions of the GI tract. These basic relationships persist, but the adult anatomy appears complex because of four developments: (1) rotation of the abdominal foregut tube 90 degrees clockwise, (2) development of the greater omentum and lesser peritoneal sac from the dorsal mesentery of the abdominal foregut, (3) rotation of the midgut 270 degrees around the superior mesenteric artery, and (4) tremendous growth of the midgut intestines.

PLAN FOR THE INGUINAL CANAL

The testis begins development between parietal peritoneum and the muscles and fascia of the abdominal wall, but must end up in the scrotum, an evagination of the superficial body wall. The testis forms the inguinal canal by pushing its way through the deep body wall. The layers of the wall contribute to the coverings of the spermatic cord of vessels, nerves, and lymphatics supplying the testis.

TIMELINE



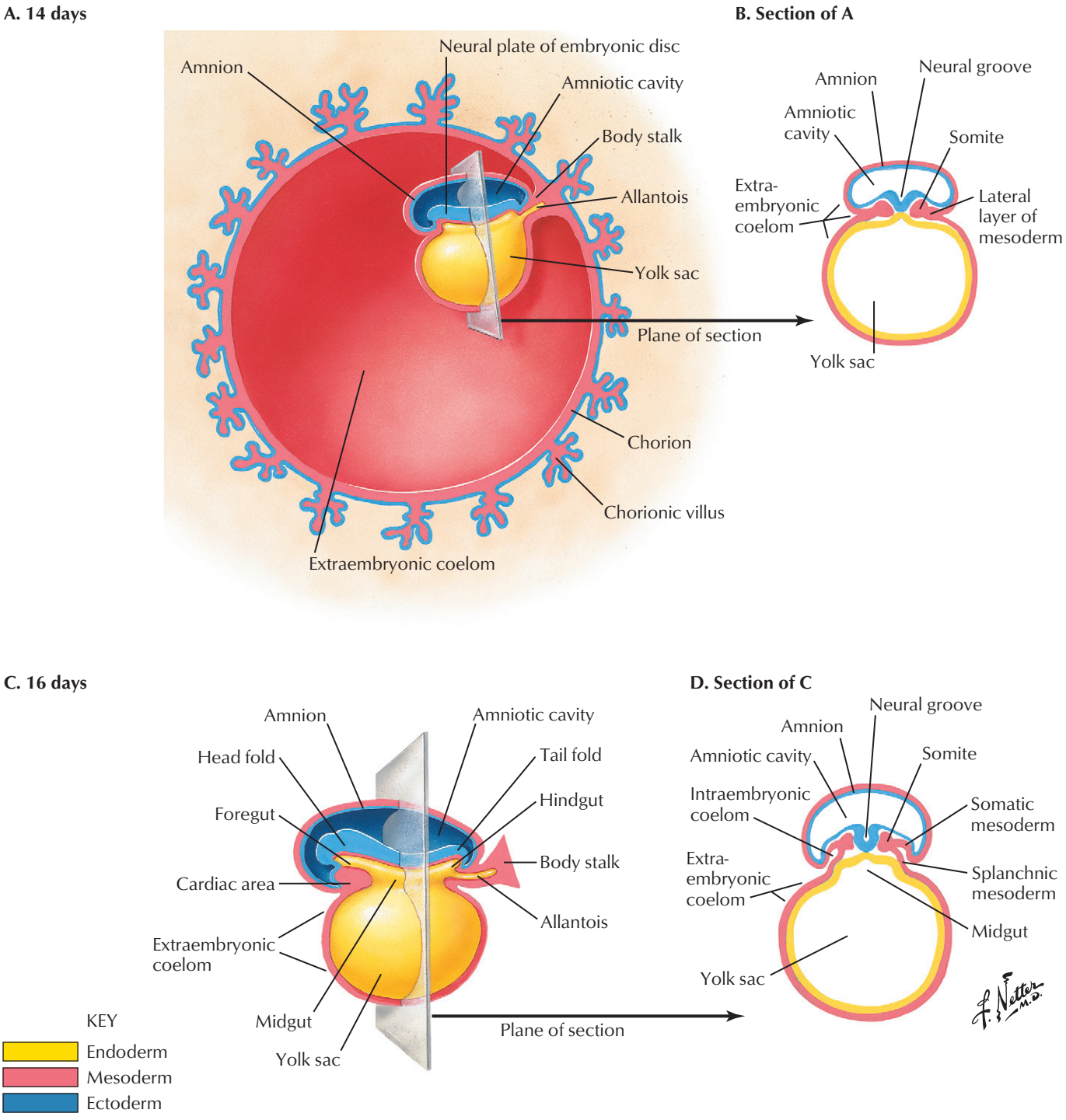


FIGURE 6.1 EARLY PRIMORDIA

The GI system develops from the endoderm of the gastrula and mesoderm from the lateral plate. The lateral plate becomes hollow to form primitive peritoneal and pleural coelomic cavities. As a result, the lateral plate mesoderm divides into somatic and splanchnic components. The splanchnic component lines the endoderm to form splanchnopleure, the primordium of the GI tract.

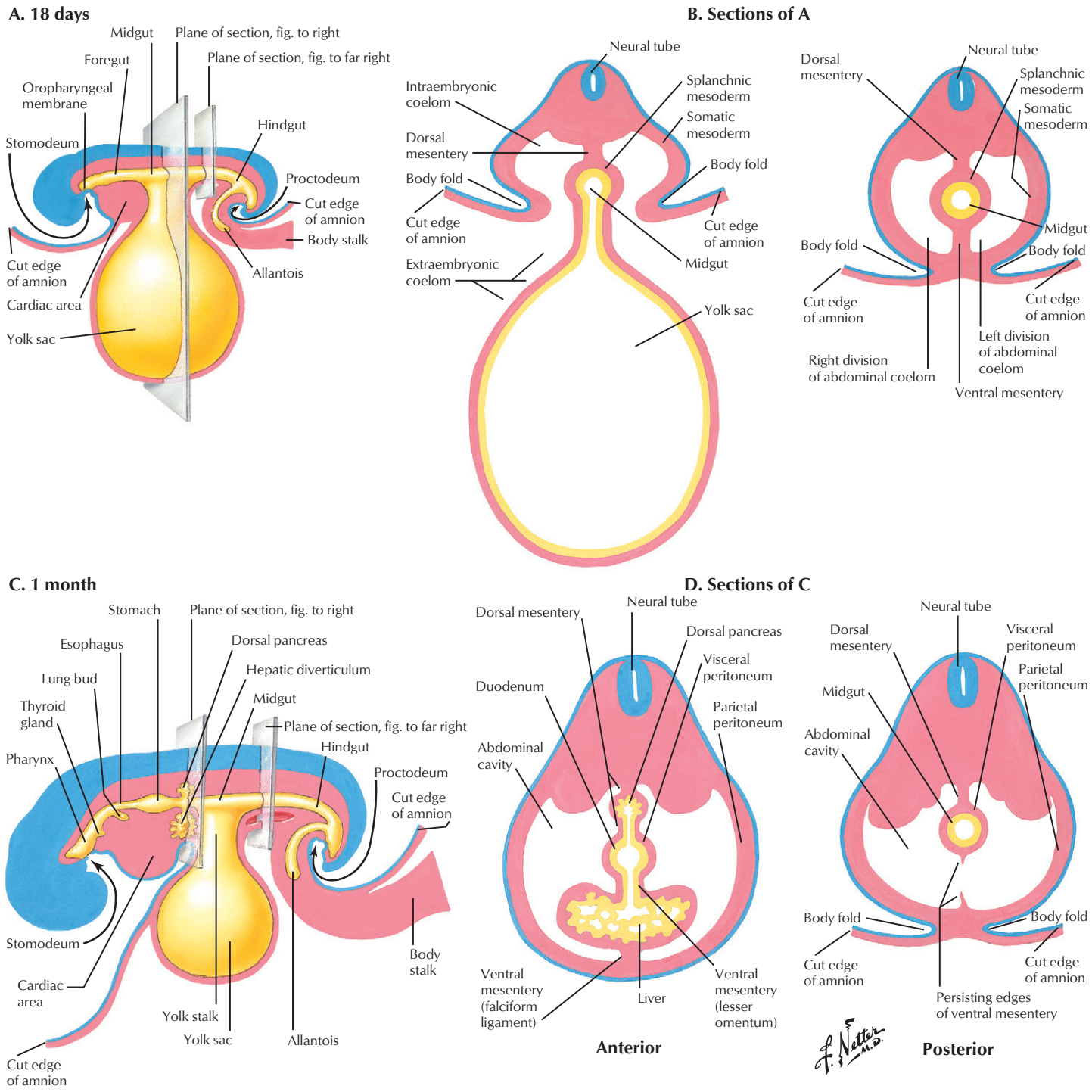


FIGURE 6.2 FORMATION OF THE GUT TUBE AND MESENTERIES

As the trilaminar disc of the gastrula folds into a cylinder, the splanchnopleure is shaped into a tube with a foregut extending into the head region, a midgut in wide communication with the yolk sac, and a hindgut extending into the tail. It is suspended by dorsal and ventral mesenteries flanked on either side by the coelomic cavities. The lateral plate mesoderm lining these cavities differentiates into the simple squamous epithelium of peritoneum (and pleura). Visceral peritoneum covers the mesenteries and GI organs; parietal peritoneum lines the inner surface of the body wall. By the end of the first month, organ buds grow from the gut tube, and the ventral mesentery of the midgut and hindgut disappears.

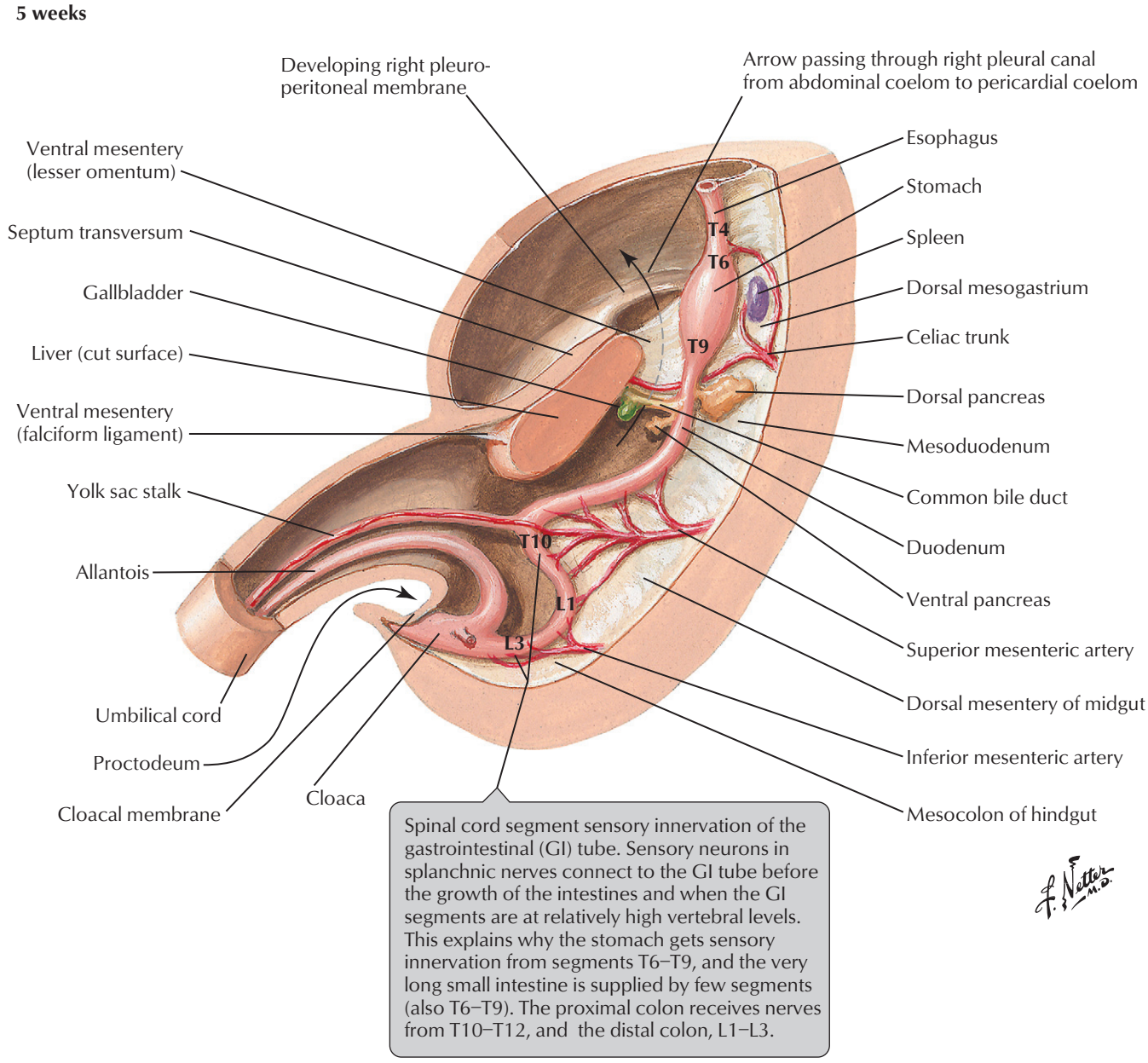


FIGURE 6.3 FOREGUT, MIDGUT, AND HINDGUT

By week 5, the yolk sac is compressed into the umbilical cord as a thin stalk. The ventral mesentery of the midgut and hindgut is gone, and the left and right peritoneal cavities communicate as a single abdominal cavity lined by the **greater peritoneal sac** of parietal peritoneum. The pleuroperitoneal membranes are separating the peritoneal and pleural cavities, and the foregut organ buds are elaborating. The abdominal foregut retains its ventral mesentery (ventral mesogastrium or lesser omentum); its free edge contains the common bile duct component of the portal triad.

The abdominal foregut, midgut, and hindgut each have their own artery off the aorta:

Foregut: celiac trunk
Midgut: superior mesenteric artery
Hindgut: inferior mesenteric artery

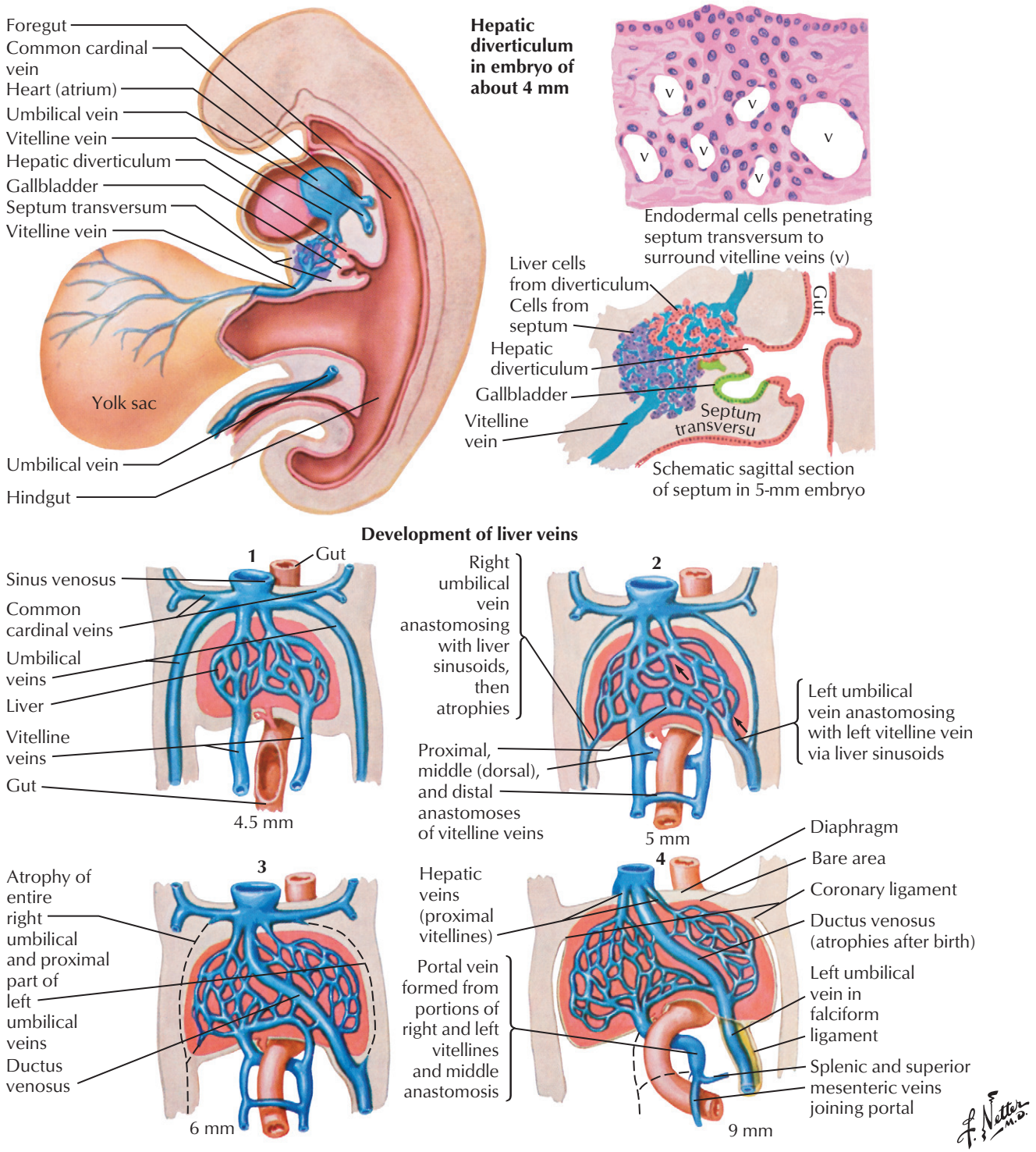


FIGURE 6.4 ABDOMINAL VEINS

Converging on the sinus venosus of the developing heart are the **common cardinal veins** with embryonic blood, the **umbilical veins** carrying oxygenated blood from the placenta, and the **vitelline veins** from the yolk sac. The vitelline veins pass through the developing liver, where they form a network of liver sinusoids. The remainder of the intraembryonic portion of the vitelline veins becomes most of the **hepatic portal system** of veins draining the gut. The right umbilical vein and proximal segment of the left disappear; the remaining part of the left umbilical vein anastomoses with the liver sinusoids to form a liver shunt into the inferior vena cava, the **ductus venosus.** After birth it becomes the fibrous **ligamentum venosum.**

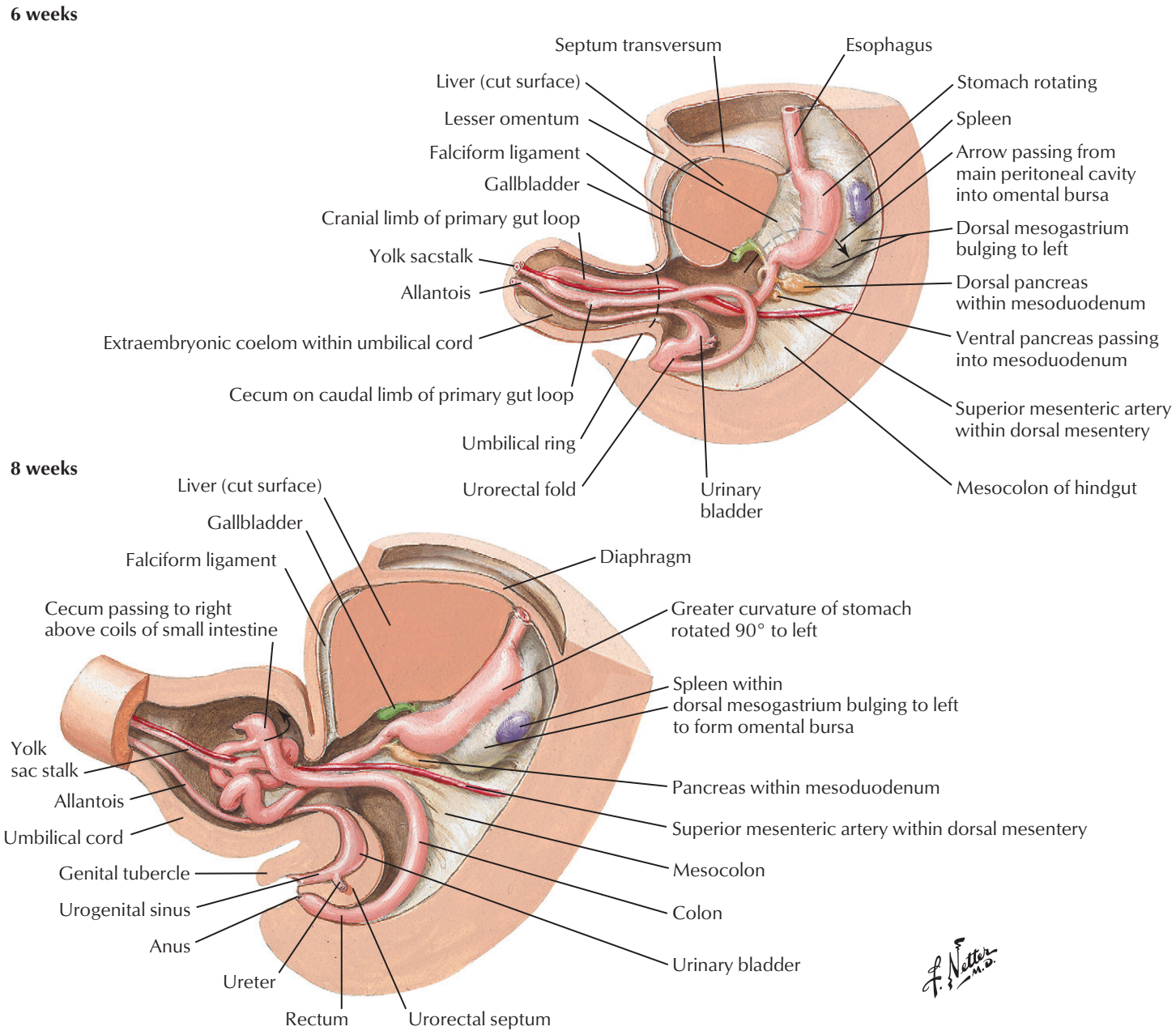


FIGURE 6.5 FOREGUT AND MIDGUT ROTATIONS

Near the end of week 8, two major events occur. The midgut grows so rapidly, it extends into the umbilical cord and begins to rotate around the superior mesenteric artery. Also, the foregut rotates 90 degrees around its long axis as the enlarging liver in the **ventral mesogastrium** (lesser omentum) moves to the right and the **dorsal mesogastrium** (greater omentum) begins to bulge to the left. This bag of dorsal mesentery will grow extensively to form the **lesser peritoneal sac** (the **omental bursa**). The greater peritoneal sac communicates with the lesser peritoneal sac under the ventral mesogastrium through the **epiploic foramen** of Winslow (dashed arrow in plate).

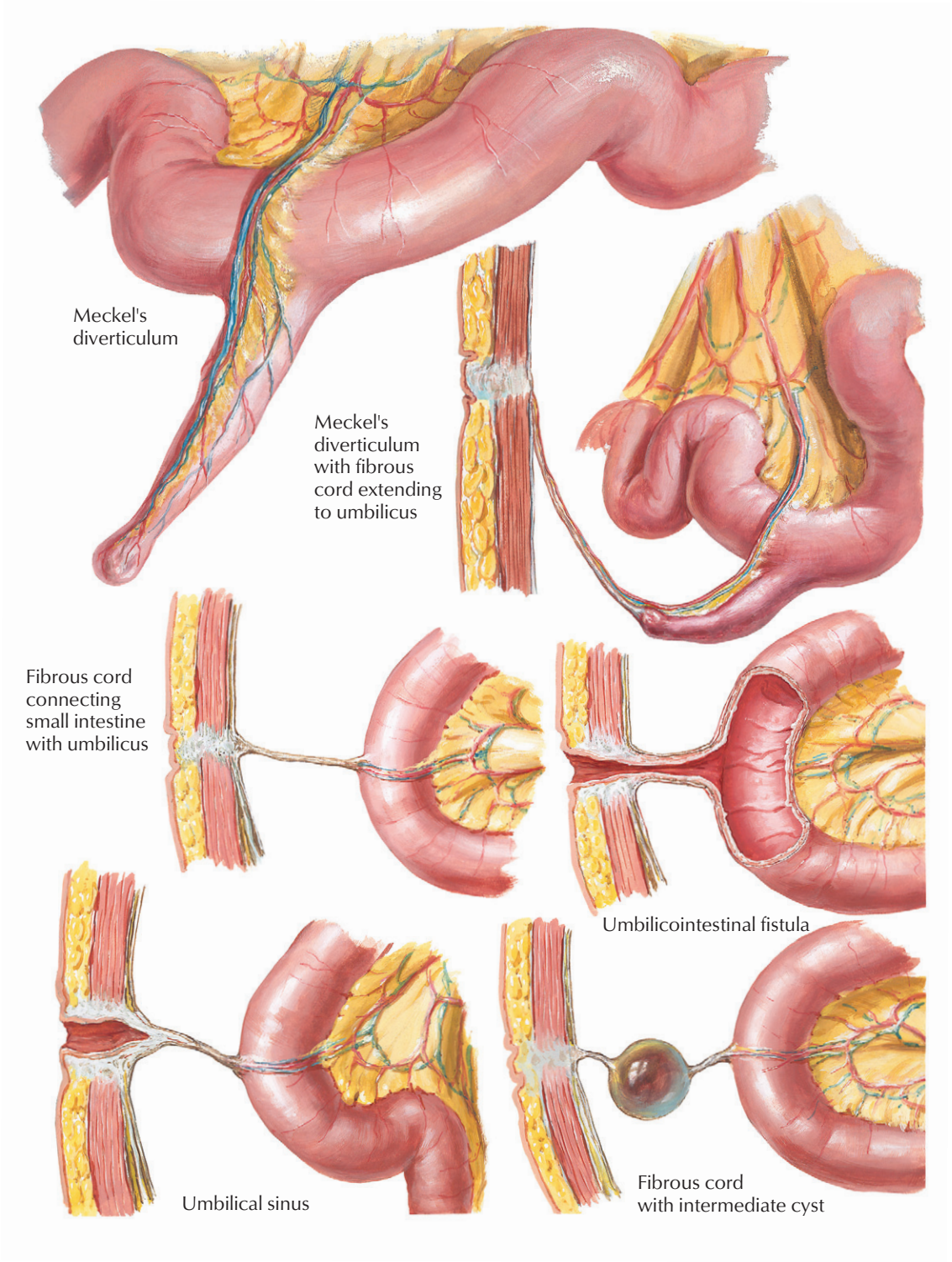


FIGURE 6.6 MECKEL'S DIVERTICULUM

The yolk sac is initially in wide communication with the midgut. It becomes compressed into the umbilical cord when the gastrula folds into the cylindrical embryo. The stalk of the yolk sac may persist as a diverticulum off the ileum (midgut) or a cord from ileum to umbilicus with varying degrees of the persistence of the yolk sac lumen. The cord may be fibrous all the way (no lumen), or it may contain a sinus, cyst, or fistula.

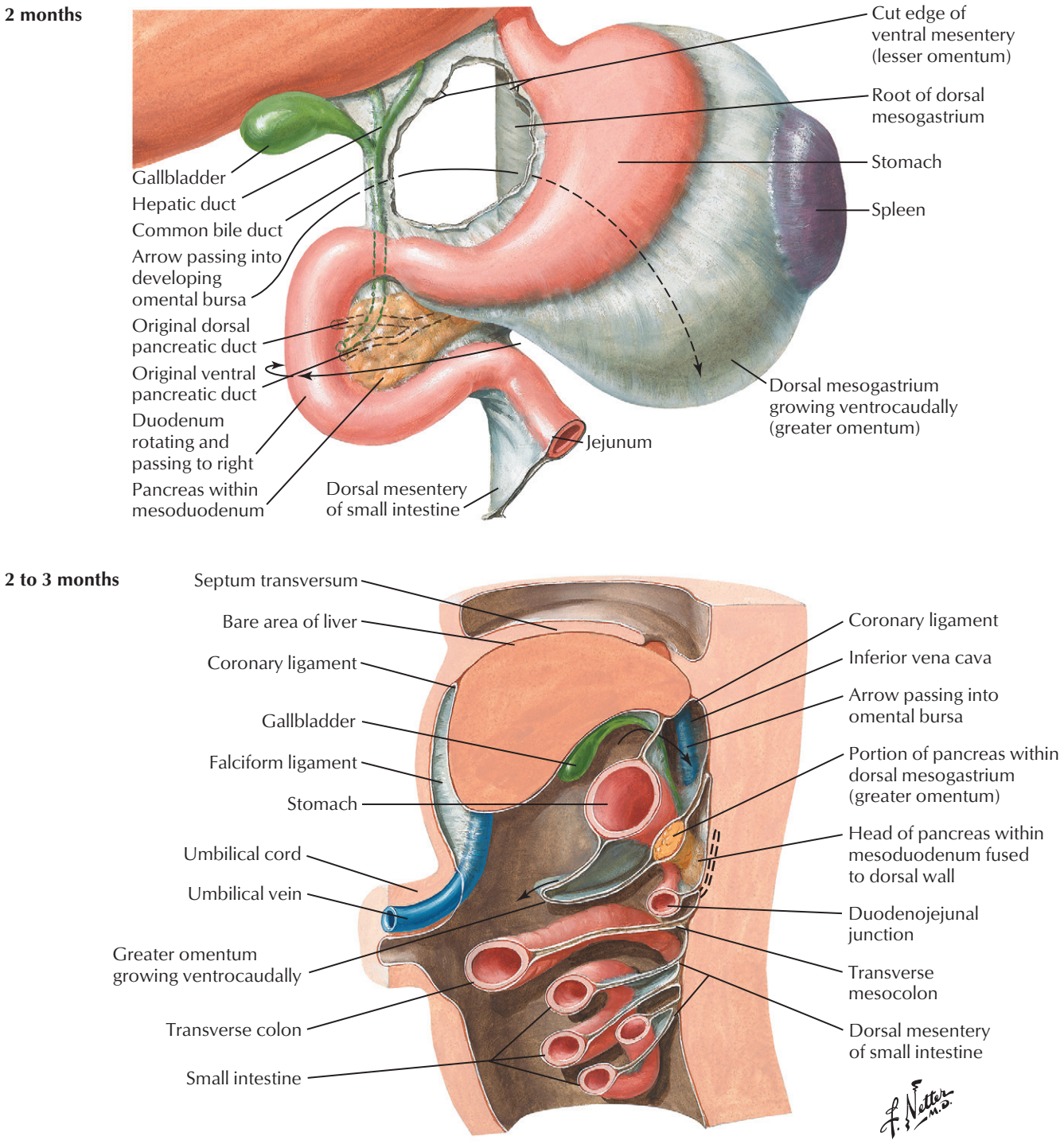


FIGURE 6.7 LESSER PERITONEAL SAC

The upper figure shows the lesser peritoneal sac of dorsal mesogastrium growing to the left and the ventral mesogastrium extending to the right. A hole is cut in the lesser omentum to expose the root of the dorsal mesogastrium in the midline. The lower figure is a sagittal section that emphasizes the caudal and ventral growth of the lesser sac toward the transverse colon. Both figures have arrows passing through the epiploic foramen into the omental bursa of the lesser sac. The surgical epiploic foramen is under the free edge of the lesser omentum; the true epiploic foramen is in the midline.

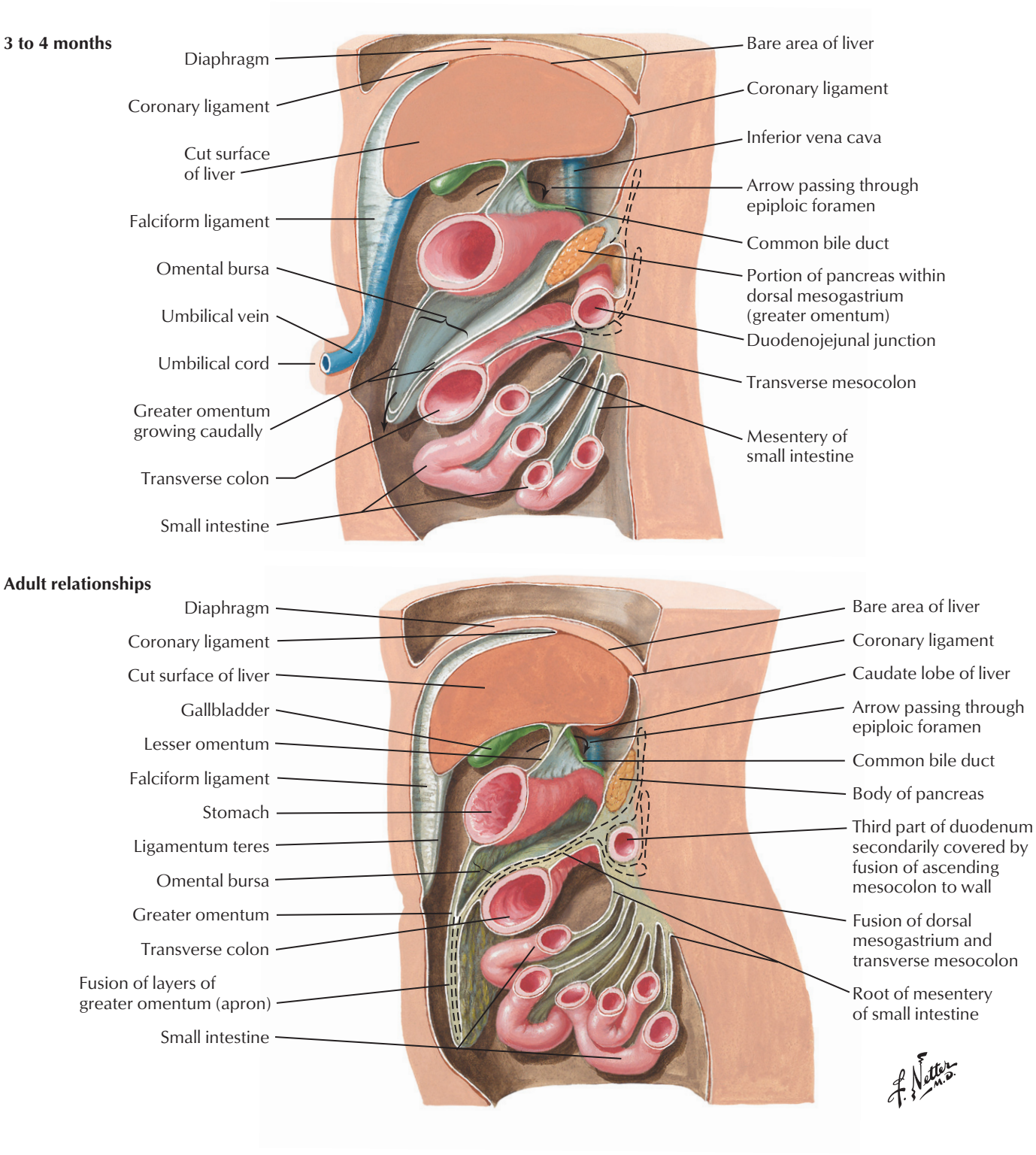


FIGURE 6.8 INTRODUCTION TO THE RETROPERITONEAL CONCEPT

By 4 months, the lesser sac begins to drape over the transverse colon. With growth of the intestines, the pancreas and duodenum are pressed against the body wall so that it appears they are outside the abdominal cavity in a **retroperitoneal** location (superficial to parietal peritoneum). Because they begin development in a mesentery, they are said to be **secondarily retroperitoneal.**

Primarily retroperitoneal organs: aorta, inferior vena cava, kidneys, suprarenal glands, urinary bladder, prostate, vagina, rectum

Secondarily retroperitoneal organs: pancreas, duodenum, ascending and descending colon

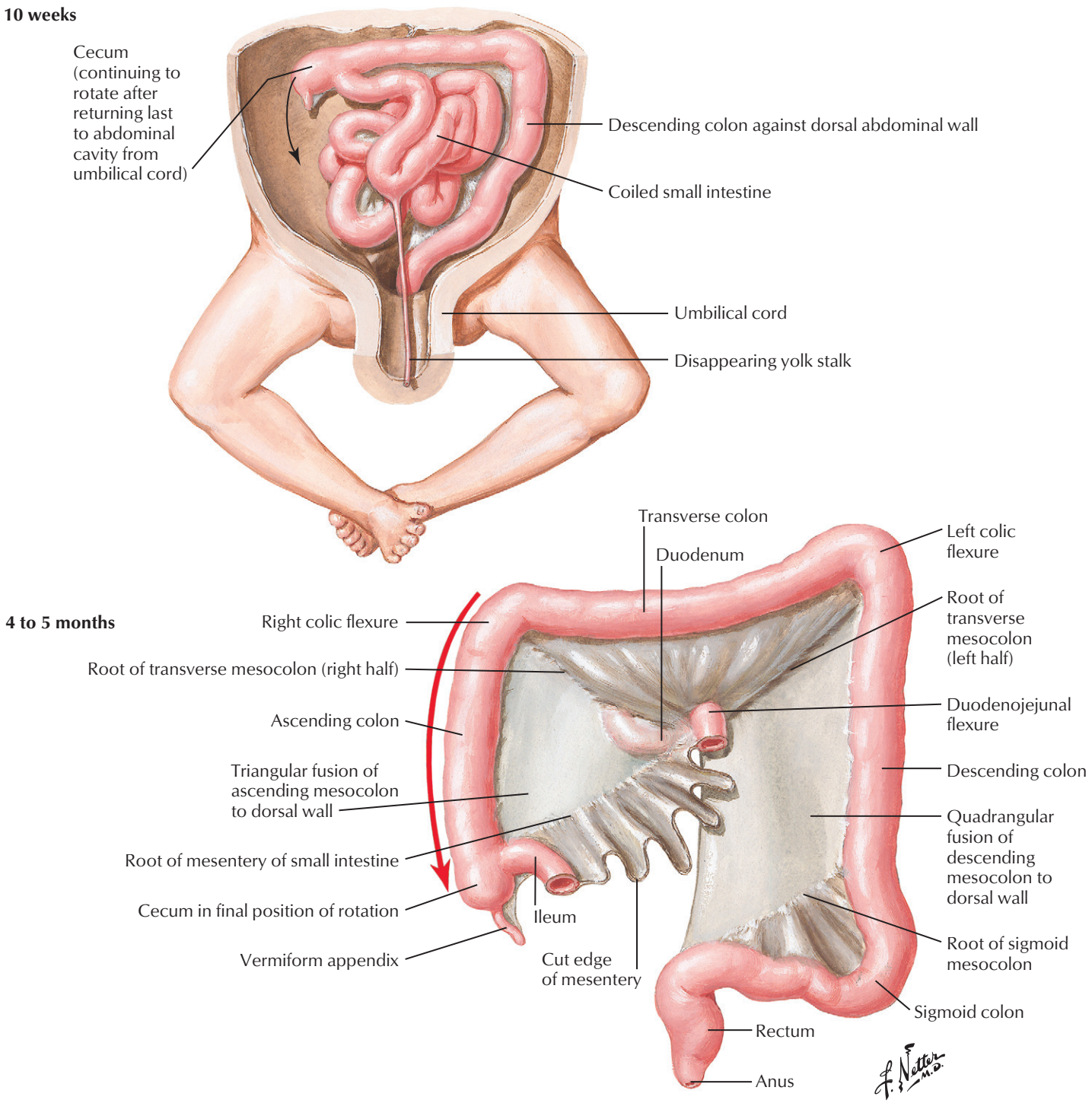


FIGURE 6.9 MIDGUT LOOP

By week 10, the intestines have returned to the abdominal cavity, and by week 20, the midgut has completed its 270-degree loop. The midgut consists of most of the duodenum, the jejunum, the ileum, the ascending colon, and most of the transverse colon. With growth of the small intestines, the ascending and descending colon are pushed against the body wall in a secondarily retroperitoneal location like the pancreas and duodenum. The small intestine, transverse colon, and sigmoid colon are still freely suspended by mesenteries in the abdominal cavity (peritonealized).

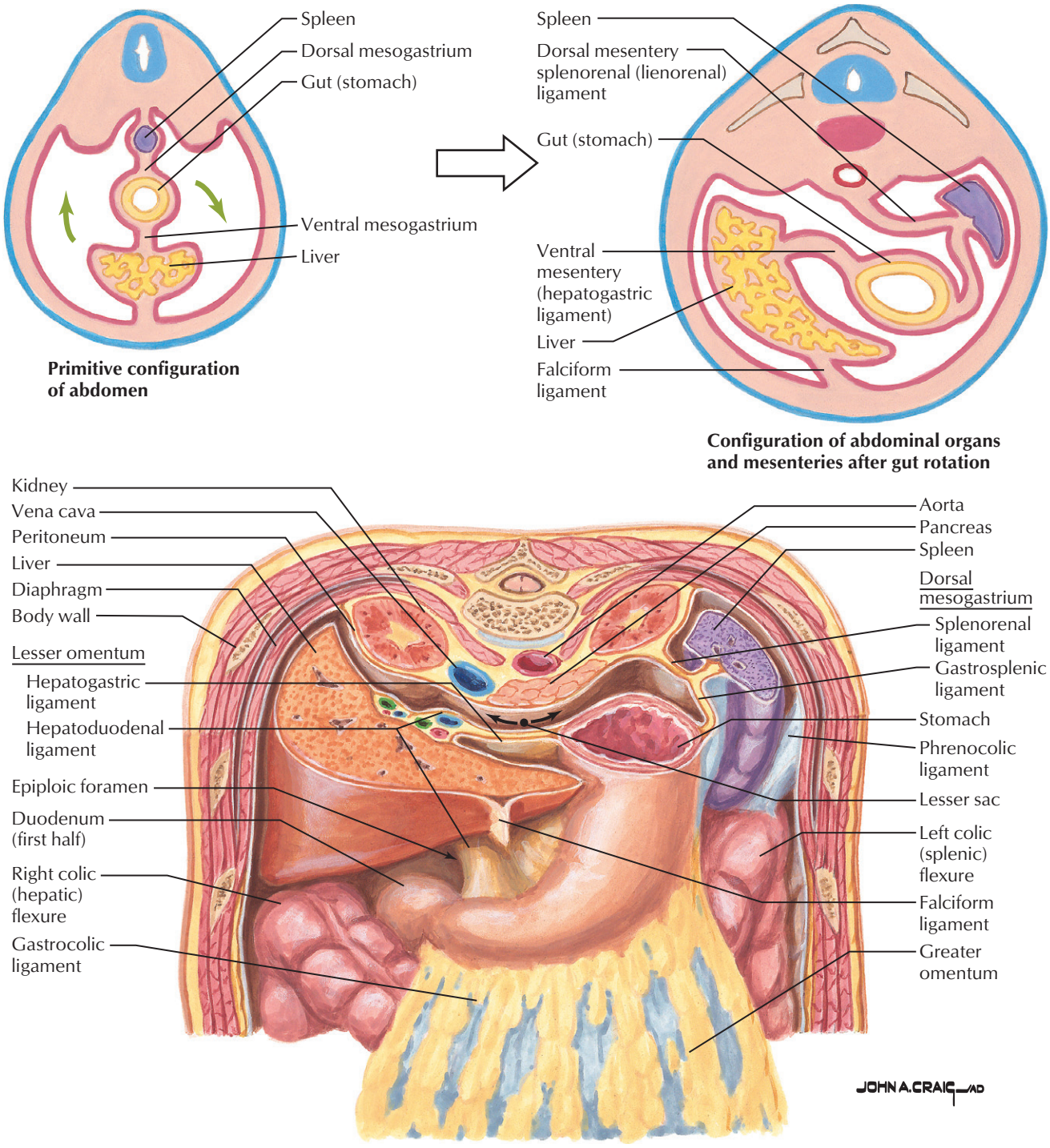


FIGURE 6.10 ABDOMINAL LIGAMENTS

After the rotations of the foregut and midgut and growth of the dorsal mesogastrium (lesser peritoneal sac), the initially straight mesenteries of the abdominal foregut are in a very convoluted, S-shaped arrangement from ventral to dorsal body wall. They are referred to as "ligaments," named by their shape or the organs they connect. Other types of ligaments are adhesions of mesenteries involving the transverse colon (phrenicocolic, gastrocolic, and hepatocolic ligaments) or fibrous cords (round ligament of the liver, ovarian ligament, and round ligament of the uterus). Note the organs that are **primarily retroperitoneal**—the kidneys, suprarenal glands, aorta, and inferior vena cava.

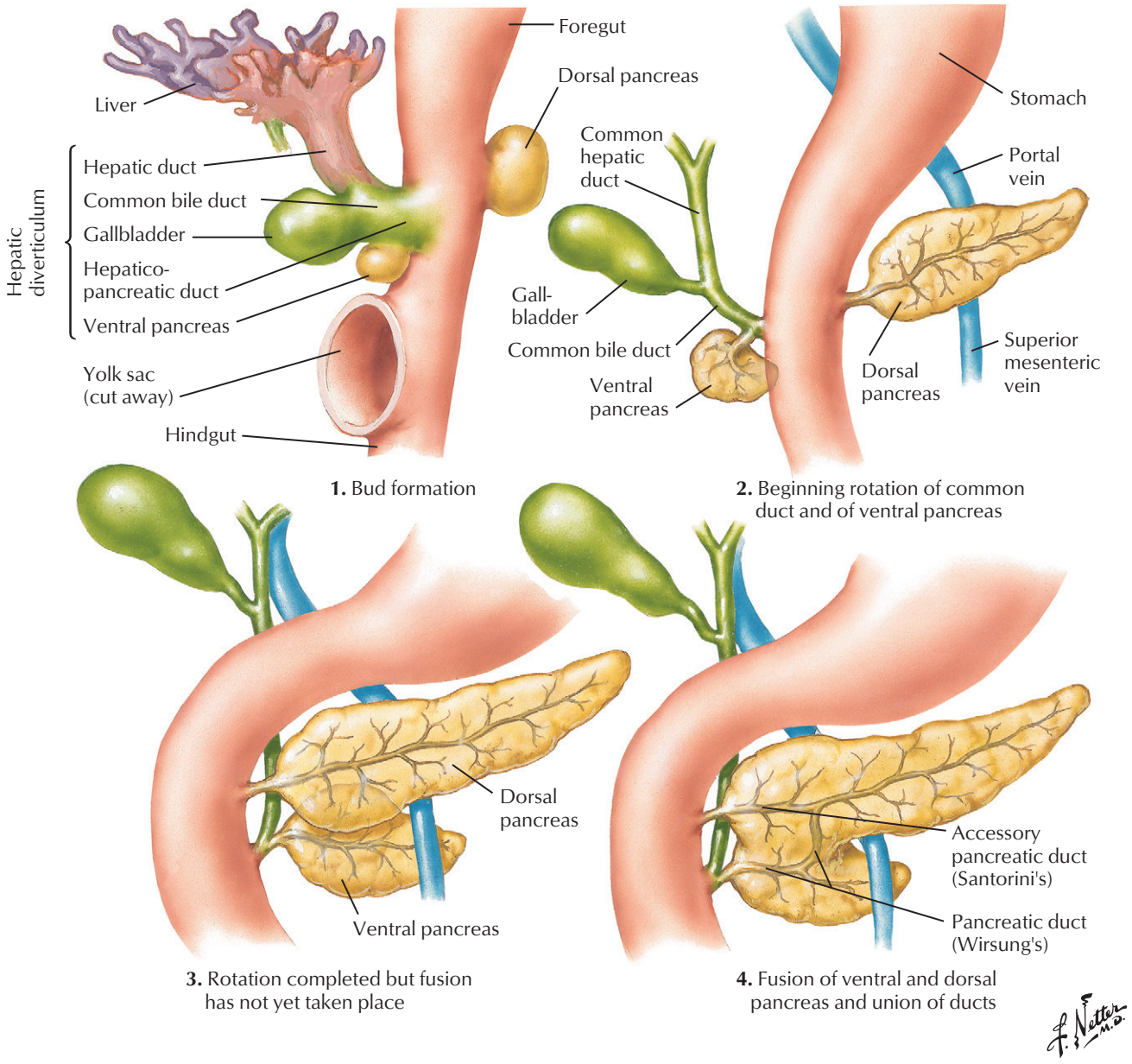
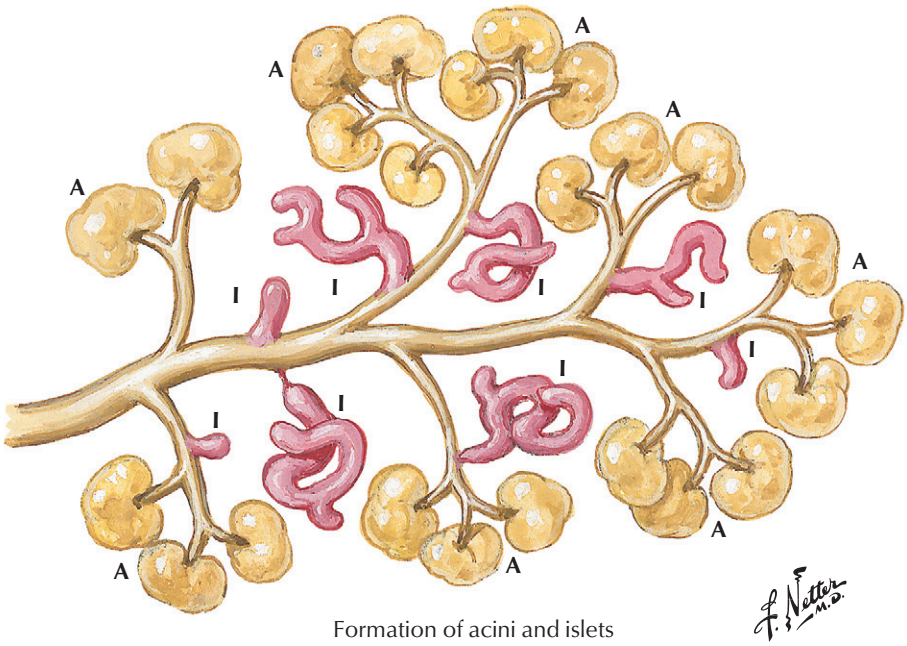
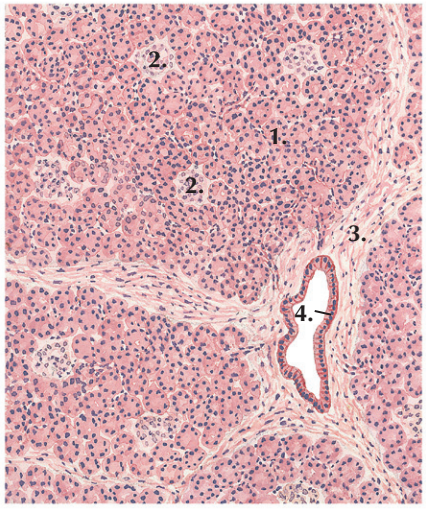


FIGURE 6.11 ABDOMINAL FOREGUT ORGAN DEVELOPMENT

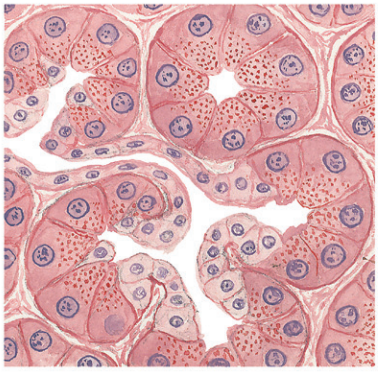
Growing off the abdominal foregut are a **dorsal pancreatic bud** and a ventral **liver diverticulum.** Sprouting from the latter are gallbladder and ventral pancreatic buds. The hepatic diverticulum gives rise to hepatocytes, gallbladder, and entire biliary apparatus. The **ventral pancreatic bud** and common bile duct migrate clockwise around the duodenum into the dorsal mesentery, where the ventral and dorsal pancreatic buds fuse. Although the ventral bud forms only part of the head of the pancreas, its duct joins that of the dorsal pancreatic bud to become the **major pancreatic duct** (of Wirsung). Vascular endothelial cells play an important role in the induction of endoderm of the liver, pancreas, and other visceral organs.



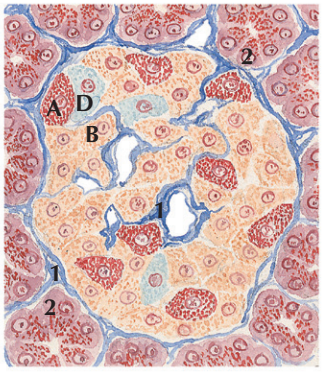
Formation of acini and islets from ducts. **A**—acini; **I**—islets in various stages of development



Low-power section of pancreas **1.** Acini, **2.** islet, **3.** interlobular septum, **4.** interlobular duct



High magnification: relationship of intercalated duct and centroacinar cells to acini



Pancreatic islet **A** (= α-), **B** (= ß-) and **D**-cells. **1.** reticulum, **2.** acini

FIGURE 6.12 DEVELOPMENT OF PANCREATIC ACINI AND ISLETS

The pancreas is an exocrine and endocrine organ with serous **acini** and vascular **islets of Langerhans** that secrete insulin, glucagon, and somatostatin. The duct system begins with **centroacinar cells** within the acini. The pancreatic buds first develop under the inductive influence of endothelial cells, the notochord, and hepatic mesenchyme. Subsequent branching and elaboration of the ducts and acini involve numerous reciprocal interactions between endoderm and mesoderm typical of the development of gut-related glands. The inductive role of the mesenchyme is nonspecific and more important for the formation of acini than ducts. The endocrine islet cells are derived from early duct epithelium.

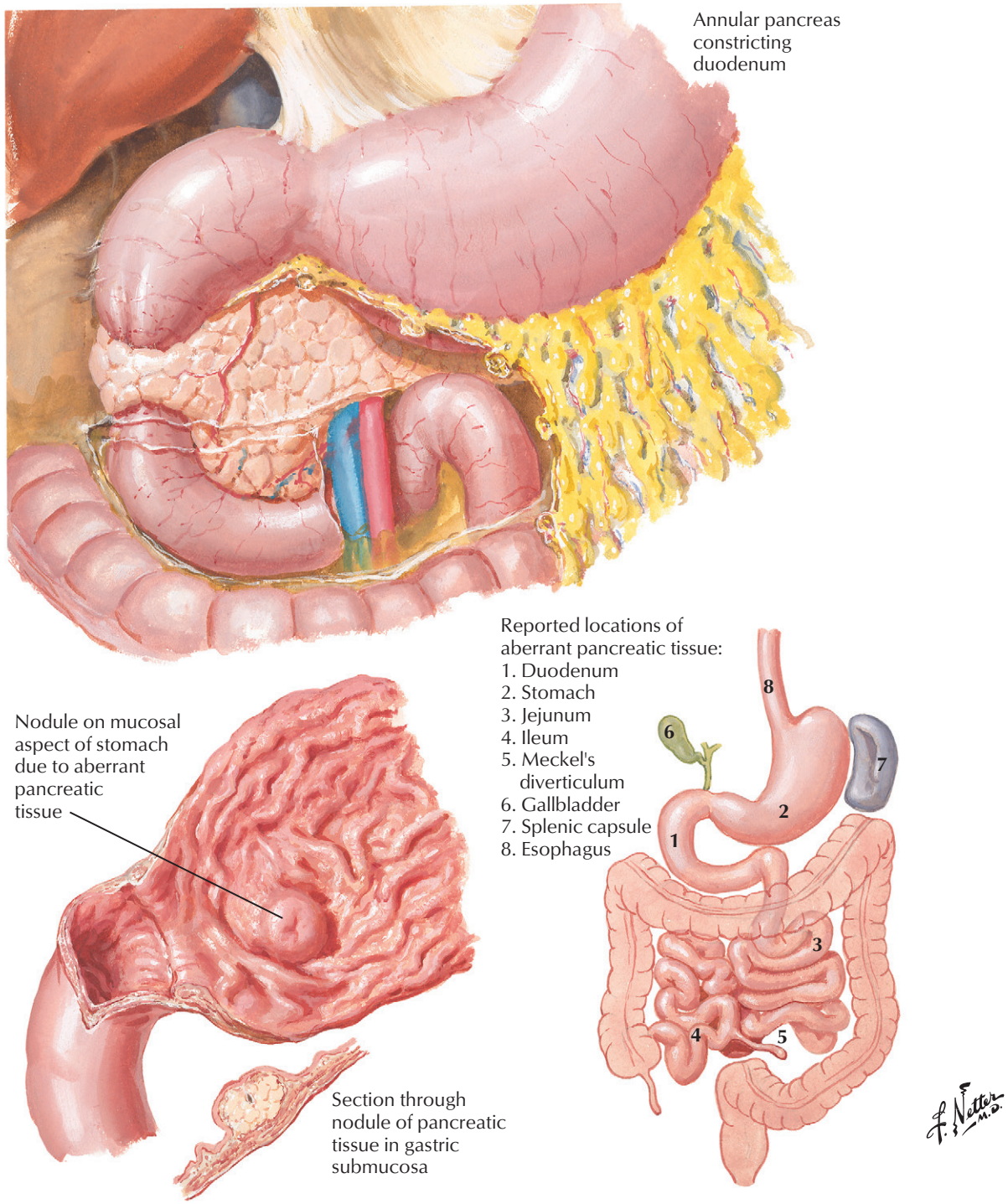


FIGURE 6.13 CONGENITAL PANCREATIC ANOMALIES

The pancreas may encircle and constrict the duodenum (top) if the ventral pancreatic bud is bifid and passes around both sides of the duodenum. Pancreatic tissue may abnormally develop in many locations in the GI tract, the spleen, and even the lungs. The sites are ranked in approximate order of frequency.

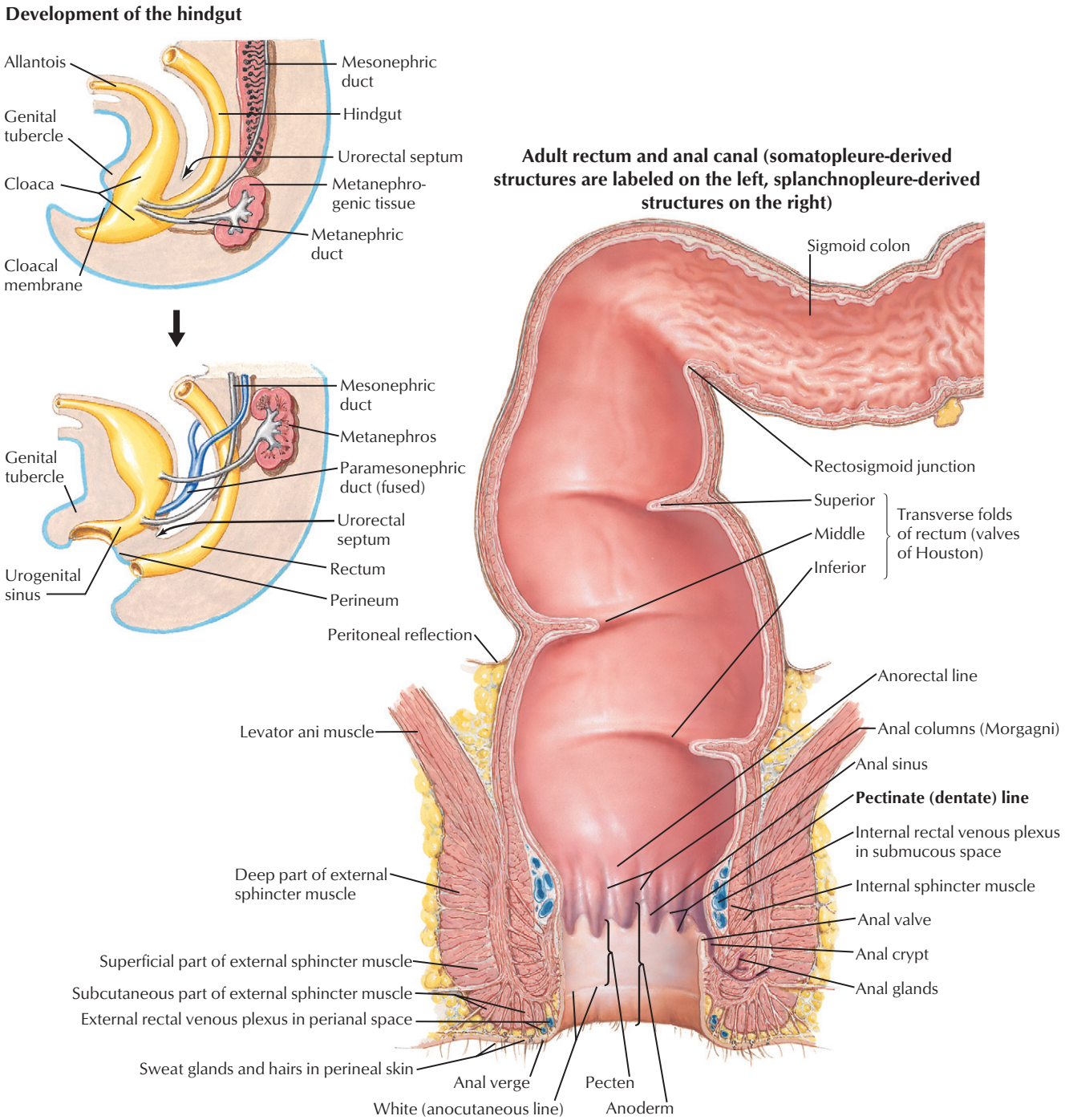


FIGURE 6.14 DEVELOPMENT OF THE HINDGUT

The **cloaca** is a chamber at the caudal end of the hindgut and allantois. The urorectal septum divides the cloaca into the rectum and urinary bladder and their related structures. The **pectinate line** of the anal canal is the site of the cloacal membrane, the junction of the gut tube (splanchnopleure) with the body wall (somatopleure). Above the line is smooth muscle of the gut (e.g., internal anal sphincter), autonomic innervation (pelvic splanchnic nerves), and blood supply related to the gut (superior rectal vessels). Below the line is skeletal muscle (external anal sphincter), somatic innervation (pudendal nerve), and blood supply via the internal iliac vessels. Routes of lymphatic drainage also differ above and below the pectinate line.

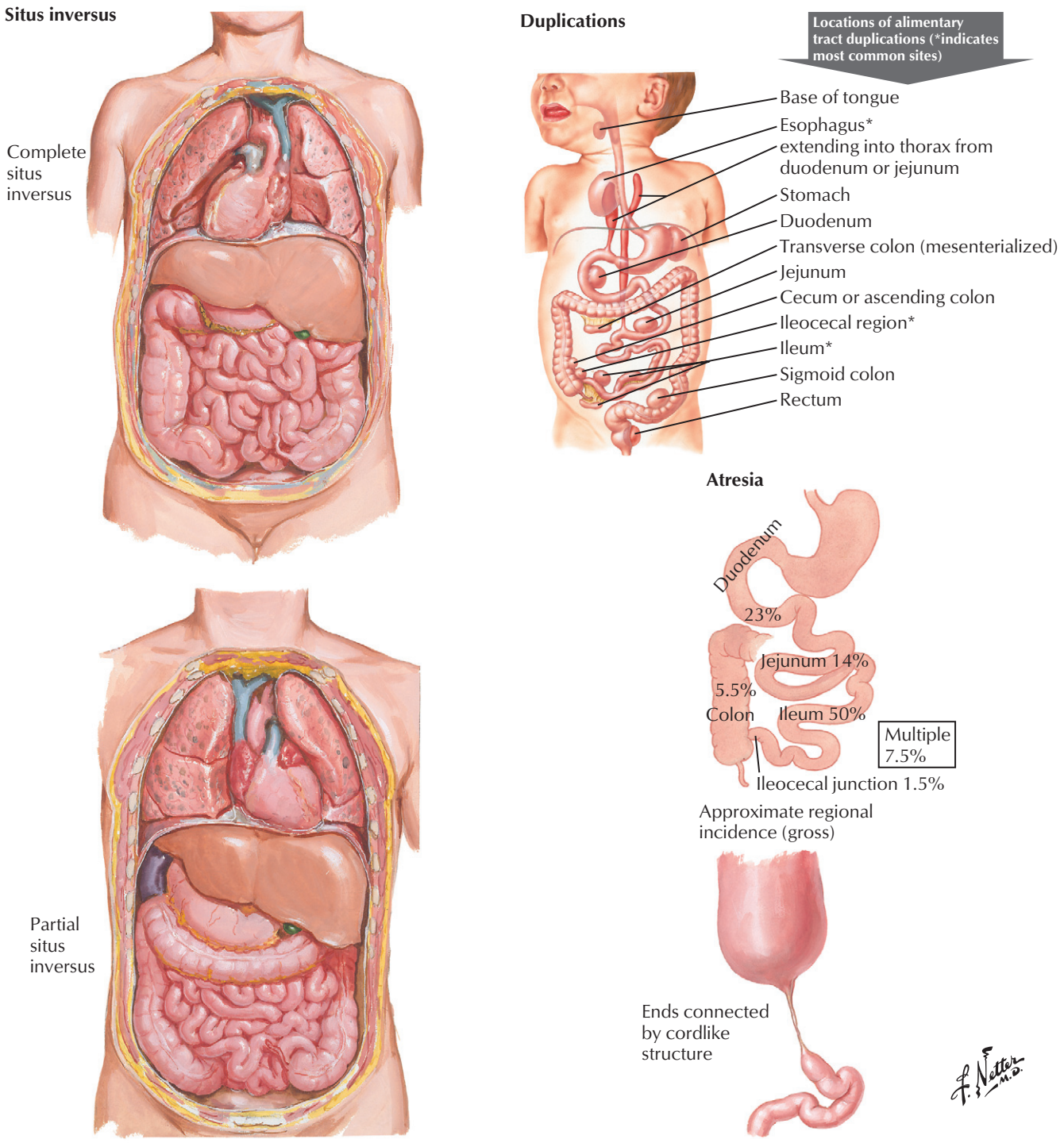


FIGURE 6.15 DUPLICATION, ATRESIA, AND SITUS INVERSUS

Anomalies of the GI tract include duplications, obstruction from atresia, and positional abnormalities. In situs inversus, developmental processes are reversed so that organs end up on the opposite side of the body than normal. Complete situs inversus affects the symmetry of the entire body. The heart bends to the right instead of to the left, the gut rotates in the opposite direction, and all organs end up in mirror-image opposite locations. Situs inversus may involve only the thorax, abdomen, or individual organs. Function is typically normal. Duplications of the GI tract can be local swellings, long blind segments of bowel, or a colon with a double lumen. Atresia variations include reduced lumen size, fibrous connections of segments, and complete discontinuity.

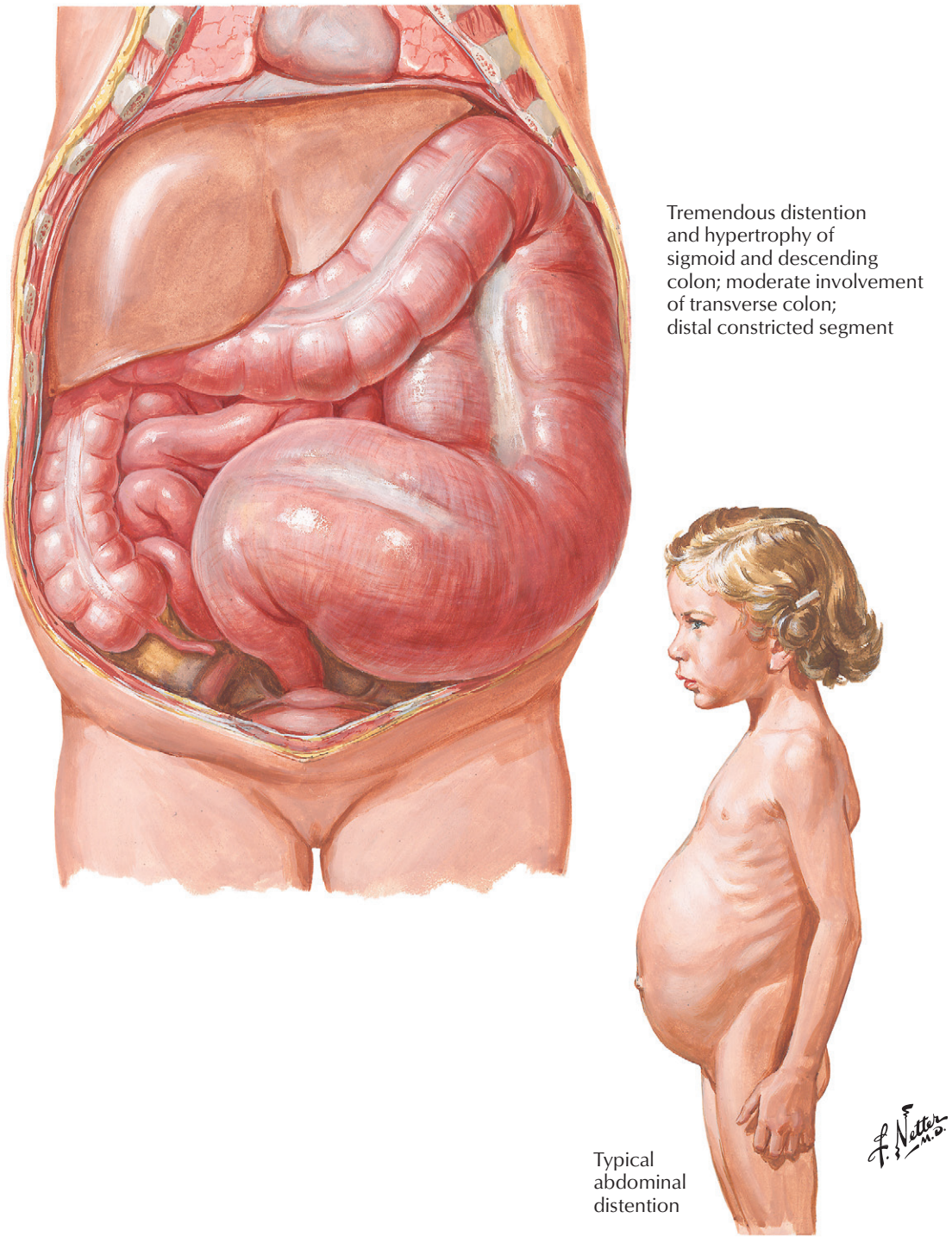
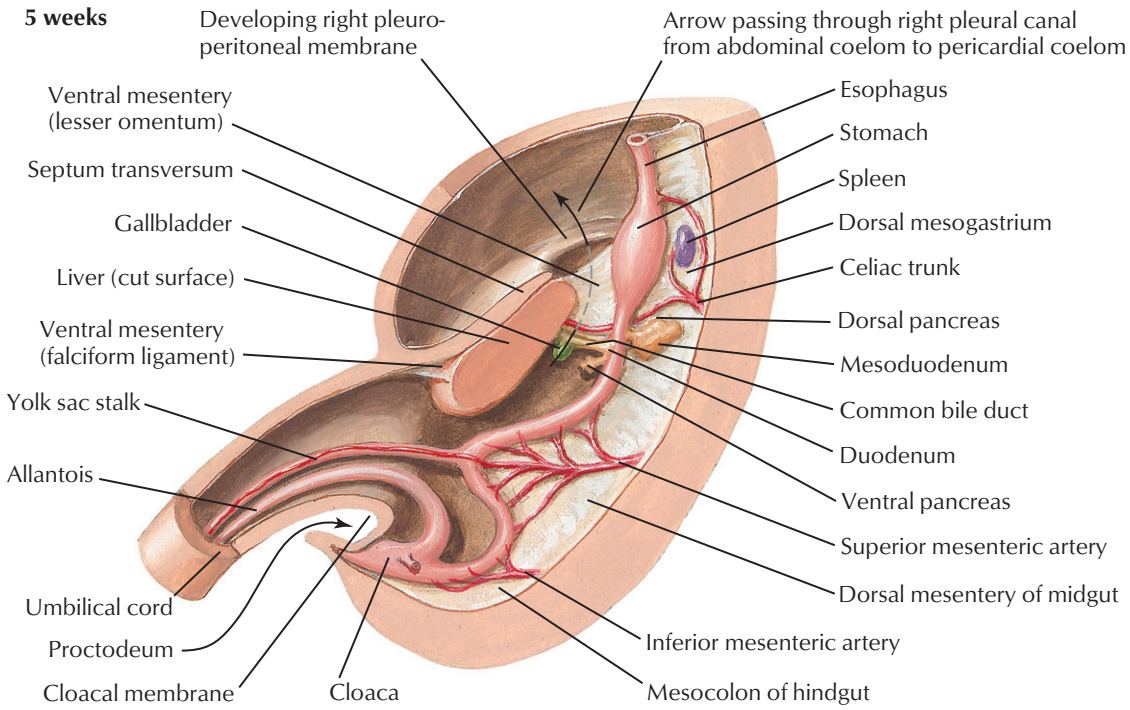


FIGURE 6.16 MEGACOLON (HIRSCHSPRUNG'S DISEASE)

Intestinal obstruction in megacolon results from impaired peristalsis and the loss of smooth muscle tone. The developmental explanation is the failure of neural crest cells to migrate into the colon to form the motor ganglia of the enteric plexus. The vagus nerve and pelvic splanchnic nerves cannot synapse within the plexus to effect contraction of the colon, and feces accumulate.



ORGANIZATION OF THE ABDOMINAL GI TRACT

	Foregut	Midgut	Hindgut
Organs	Stomach Liver Gallbladder Pancreas Spleen 1st half of duodenum	2nd half of duodenum Jejunum and ileum Cecum Ascending colon 2/3 of transverse colon	Left 1/3 of transverse colon Descending colon Sigmoid colon Rectum
Arteries	Celiac trunk: Splenic artery Left gastric Common hepatic	Superior mesenteric: Ileocolic Right colic Middle colic	Inferior mesenteric: Left colic Sigmoid branches Superior rectal
Ventral mesentery	Lesser omentum Falciform ligament Coronary/triangular ligaments	None	None
Dorsal mesentery	Gastrosplenic ligament Splenorenal ligament Gastrocolic ligament Greater omentum	Mesointestine Mesoappendix Transverse mesocolon	Sigmoid mesocolon
Motor nerve supply	Vagus	Vagus	Pelvic splanchnic nerves

FIGURE 6.17 SUMMARY OF GUT ORGANIZATION

The GI tract is a simple tube in the early embryo, and the abdominal foregut, midgut, and hindgut are distinct in their blood supply, parasympathetic innervation, and characteristics of their mesenteries. The tube loses its simple arrangement with the rotations of the foregut and midgut, the growth of the dorsal mesogastrium and formation of the lesser sac, and the tremendous growth of the intestines. As a result, the appearance of the GI tract is complicated in the adult, but the simple embryonic relationships persist.

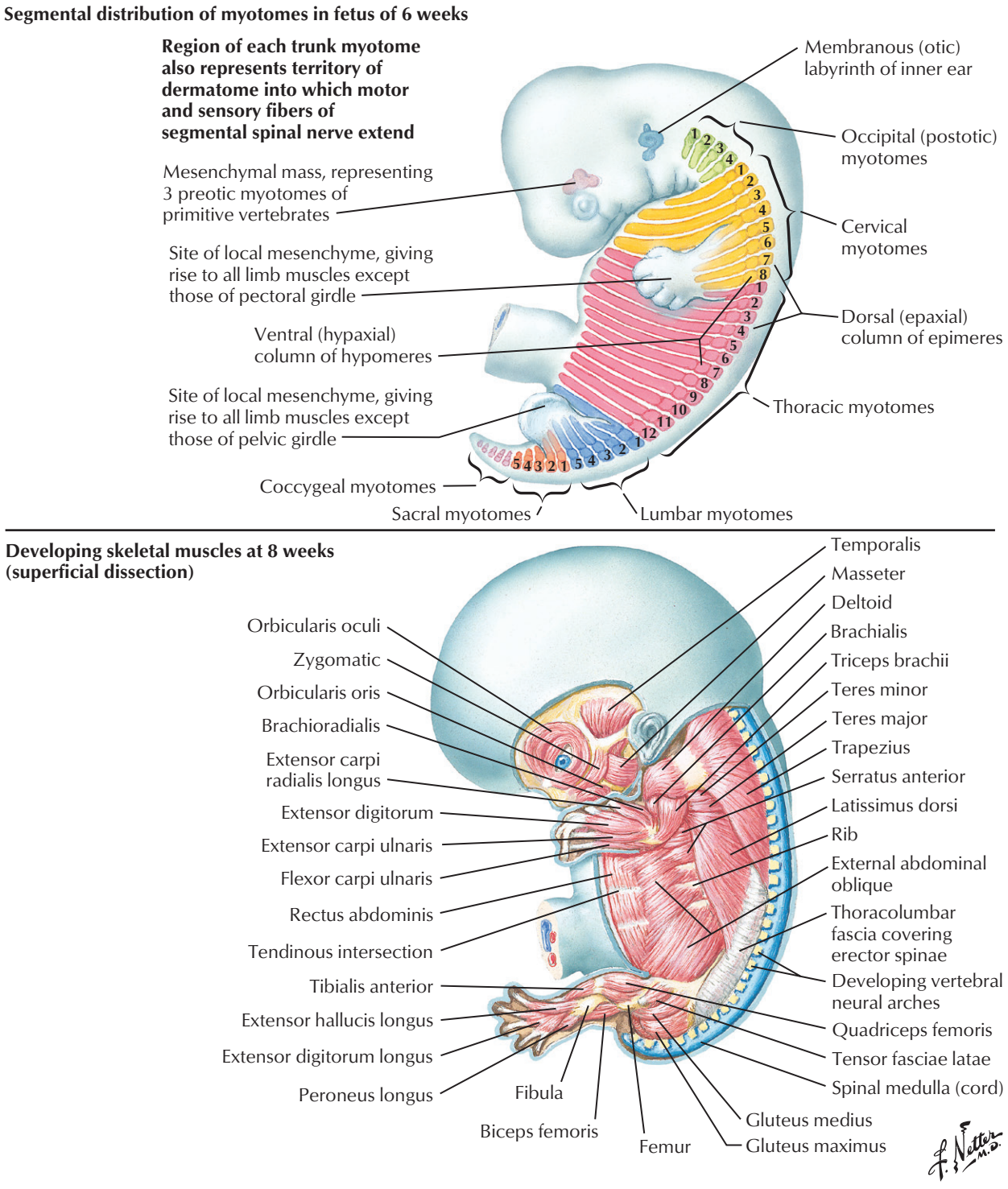


FIGURE 6.18 DEVELOPMENT OF THE ABDOMINAL WALL

Muscles of the abdominal wall develop from the hypomeres of somites from spinal segments T7 to L1, with dermatome T10 at the level of umbilicus. As with the thoracic musculature, the abdominal muscles develop in three layers. There is a single, vertical muscle anteriorly—the rectus abdominis.

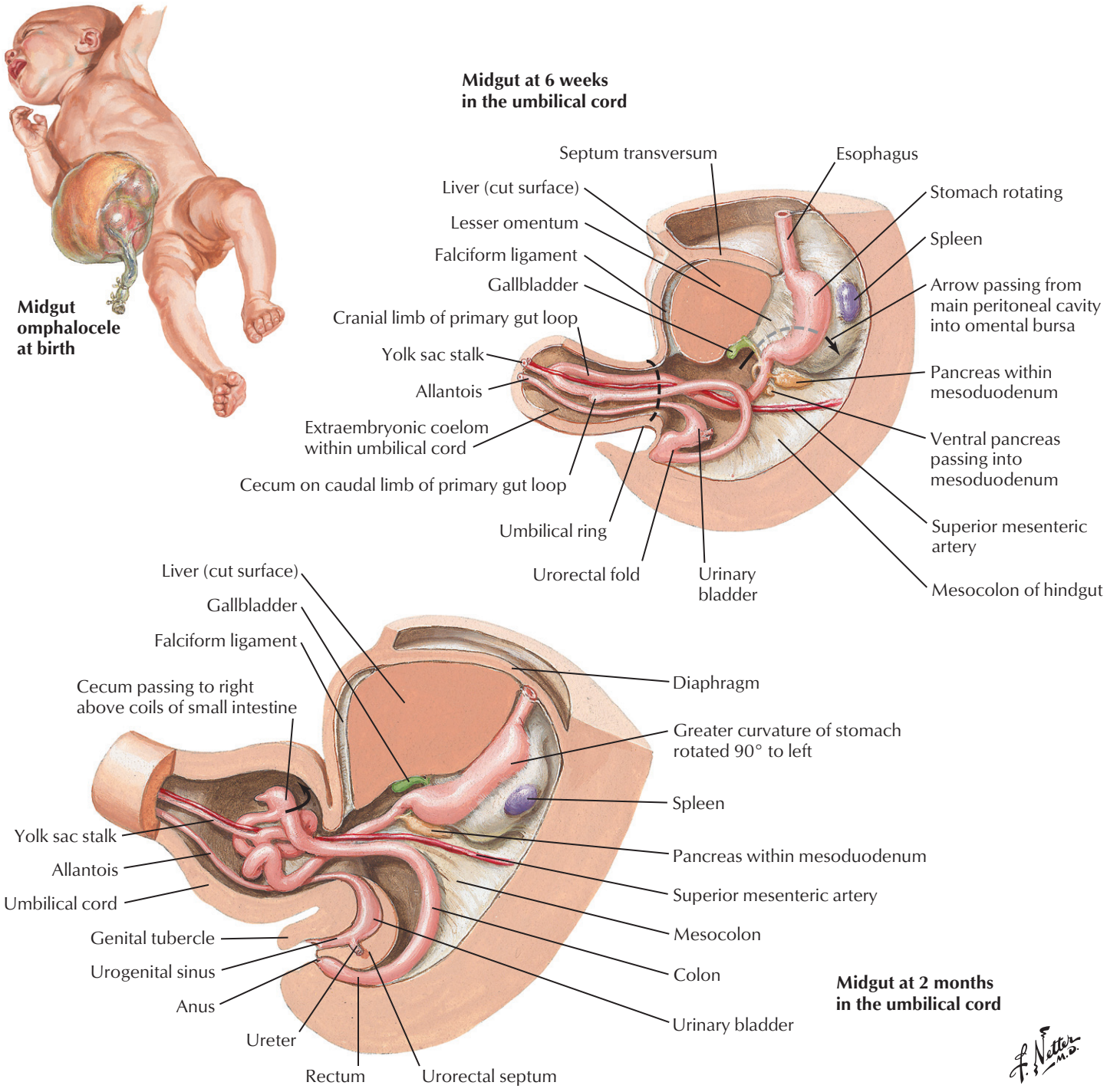


FIGURE 6.19 UMBILICAL HERNIA

A **hernia** is typically the protrusion of an internal organ in a **sac of parietal peritoneum** through a weak spot in the abdominal wall (or other location). Potential sites include the ventral midline where the left and right sides must fuse, areas where structures pass through the body wall (e.g., umbilicus, inguinal canal, diaphragm), or the relatively weak areas between muscles. Shown here is a congenital hernia of the midgut, which grows extensively in the umbilical cord at the end of the second month as a natural part of development. Sometimes it fails to return and persists as an omphalocele covered with parietal peritoneum, thin connective tissue from the umbilical cord, and amnion.

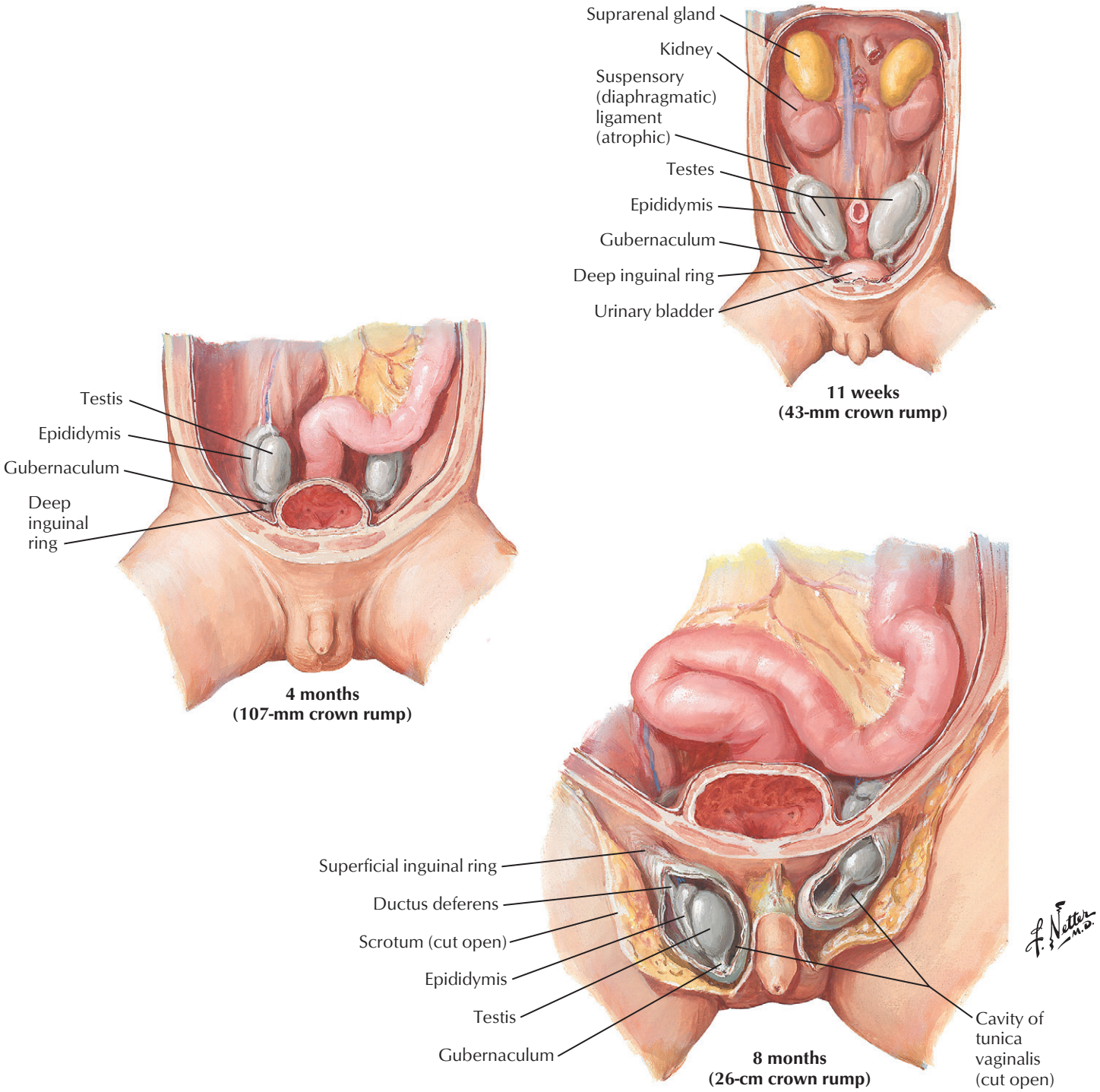


FIGURE 6.20 TESTIS DESCENT THROUGH THE DEEP BODY WALL

The testes develop from the intermediate mesoderm that develops against the parietal peritoneum deep to the abdominal wall. They must pass through the deep muscle and fascial layers via the **inguinal canal** to end up in the scrotum for the proper temperature regulation required for sperm development. The openings at each end of the inguinal canal are the **deep and superficial inguinal rings.** The testes are "guided" into the scrotum by the fibrous **gubernaculum,** and they pull their **spermatic cord** of vessels and nerves along their path of descent. They pass through the inguinal canal behind an extension of parietal peritoneum, the **processus vaginalis.** It pinches off around each testis in the scrotum as its coelomic **tunica vaginalis testis.**

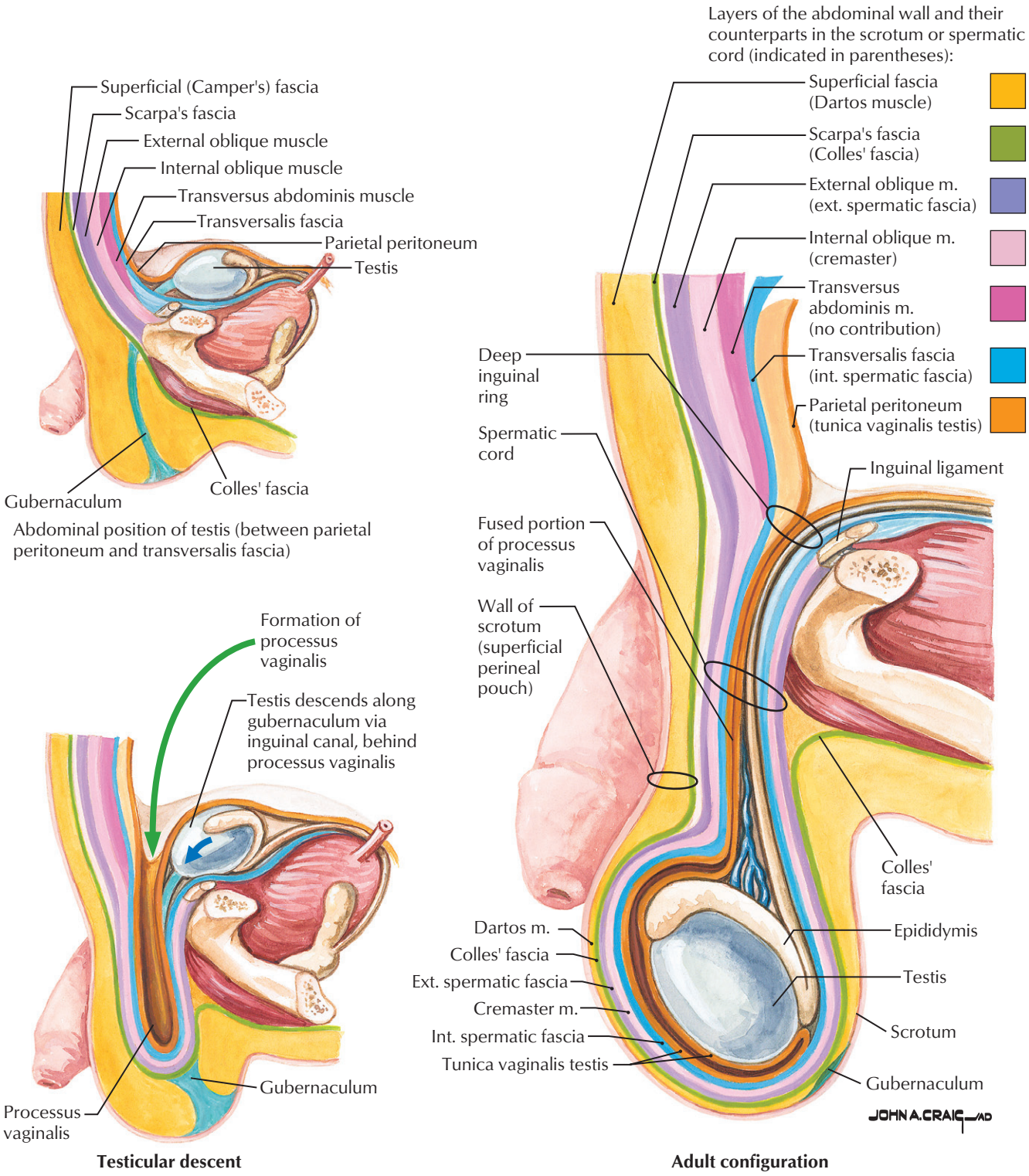


FIGURE 6.21 COVERINGS OF THE SPERMATIC CORD

As the testis passes through the inguinal canal, the layers of the deep body wall contribute to coverings of the spermatic cord (**external and internal spermatic fascia** with the **cremaster muscle** in between). The scrotum is an evagination of the superficial body wall. The superficial fascia and **Scarpa's fascia** of the latter extend into the scrotum as the **Dartos muscle** and **Colles' fascia,** respectively. Females have an inguinal canal that contains the remnant of the gubernaculum. Descent of the ovaries stops in the pelvis, and the gubernaculum attaches to the uterus. From ovary to uterus it is the **ovarian ligament,** and from the uterus through the inguinal canal it becomes the **round ligament of the uterus.**

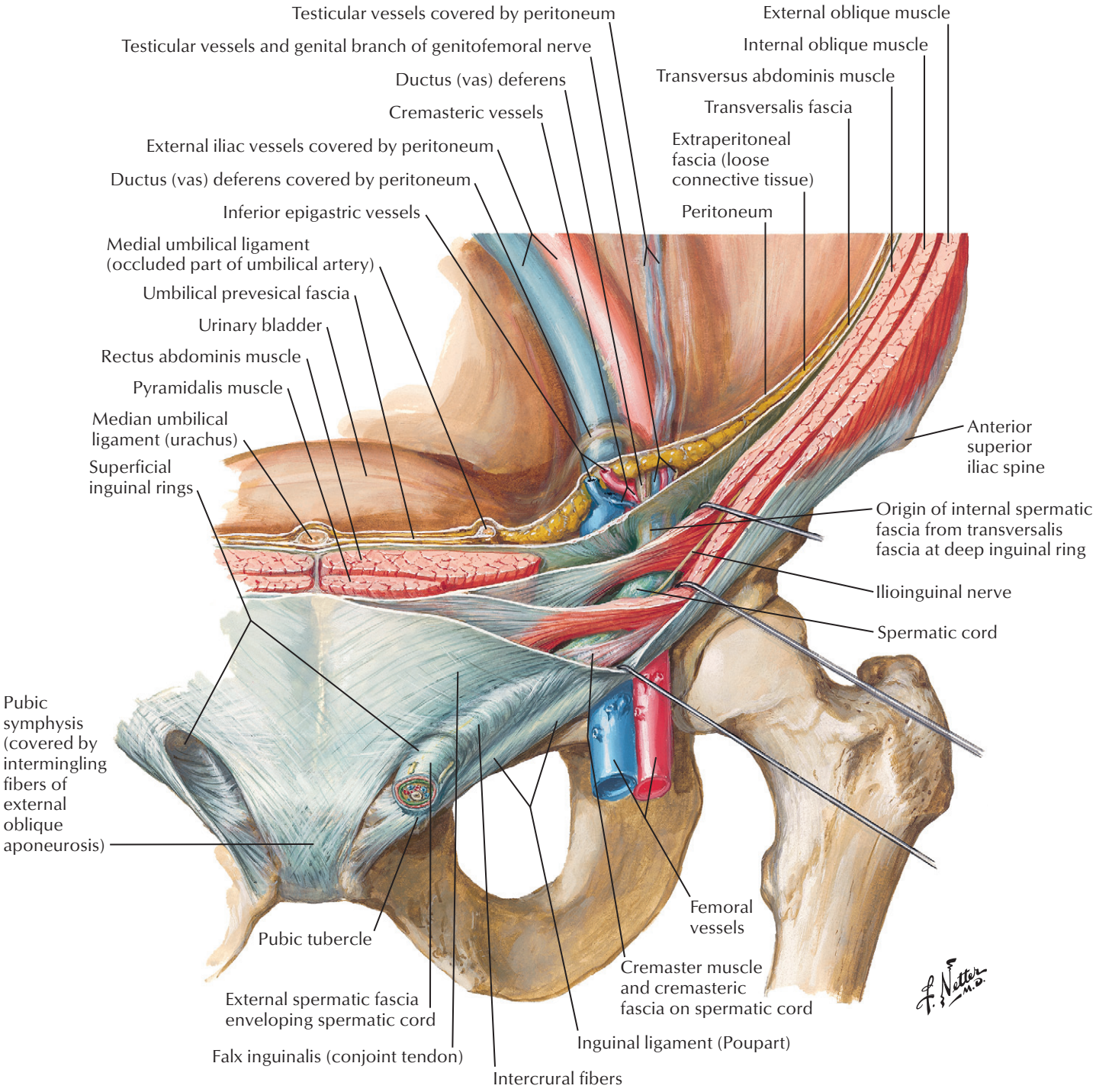


FIGURE 6.22 THE ADULT INGUINAL REGION

This figure is an anterior view of the left inguinal canal showing how the layers of the abdominal wall become the coverings of the spermatic cord. The testis begins its descent from the deepest location in the body wall just superficial to the parietal peritoneum. The first layer it encounters is the transversalis fascia that evaginates to form the internal spermatic fascia. The rim of evagination is the deep inguinal ring. The transversus abdominis muscle has no contribution to the cord. The internal oblique gives rise to the cremaster muscle, and the external oblique aponeurosis continues as the external spermatic fascia just deep to an opening in the aponeurosis, the superficial inguinal ring.

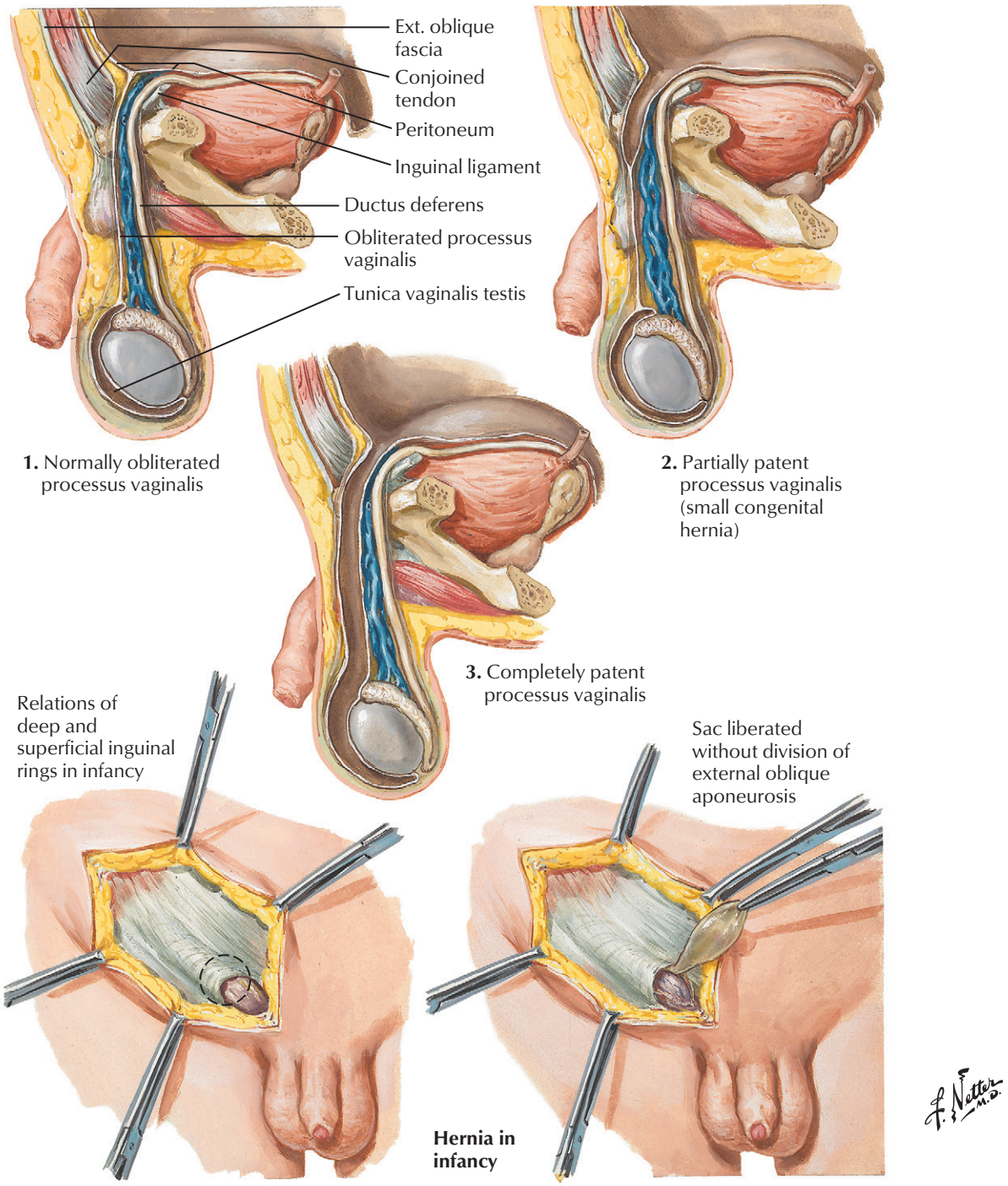


FIGURE 6.23 ANOMALIES OF THE PROCESSUS VAGINALIS

The **processus vaginalis,** a finger-like extension of parietal peritoneum into the scrotum, usually becomes obliterated as it pinches off to become the tunica vaginalis testis. It may persist either completely or in part as a ready-made hernial sac passing through the inguinal canal. This is a congenital **indirect inguinal hernia.** A section of the processus vaginalis may also persist as a cyst or hydrocele (not shown). A direct inguinal hernia passes medial to the spermatic cord and inferior epigastric vessels. It does not go through the inguinal canal, but rather forces its way through the body wall under the conjoined tendon.

Terminology

Acinus	(L., "grape") A saclike dilation or cluster of cells found in many exocrine glands.
Alveolus	(L., "hollow") Sometimes used interchangeably with *acinus*.
Biliary apparatus	The bile system. Bile is a fat emulsifier produced in the liver by hepatocytes. It is secreted into bile canaliculi that converge on larger ducts until a single common bile duct joins the pancreatic duct to empty into the duodenum. The gallbladder stores and concentrates bile.
Cloaca	(L., "sewer") Chamber at the caudal end of the hindgut and allantois that divides in most mammals into the urinary bladder and rectum and related organs and structures. Other animals retain this common urinary, GI, and genital receptacle with one external opening.
Colles' fascia	Membranous inner lining of the scrotum and perineum. It is continuous with Scarpa's fascia, the deepest layer of the superficial body wall.
Deep inguinal ring	The margin of evagination of the transversalis fascia where it becomes the internal spermatic fascia. All of the constituents of the spermatic cord (and an indirect inguinal hernia) pass through the deep ring.
Exocrine	(G., "outside" 1 "to separate") Usually refers to glands that secrete "outwardly" into a duct. Endocrine glands secrete their product "inwardly" into the bloodstream. Paracrine glands or cells secrete their product into the tissue around them to affect adjacent cells. Holocrine glands slough off cellular contents into ducts.
Greater omentum	In the embryo, it is the dorsal mesogastrium. Common use in the adult is restricted to the fused layers of the dorsal mesogastrium that cover the intestines below the transverse colon (the "apron" of the dorsal mesogastrium).
Greater peritoneal sac	Parietal peritoneum surrounding the abdominal cavity.
Gubernaculum	(L., "helm or rudder") The fibrous cord that guides the descent of the testis from the abdominal cavity to the scrotum.
Hemorrhoids	Varicose dilations of veins in the anal canal. Internal hemorrhoids are above the pectinate line and related to the gut. External hemorrhoids are below the pectinate line and associated with the body wall.
Hepatocytes	Liver cells arranged in epithelial sheets. One cell type is responsible for all of the liver's metabolic functions.
Intercalate	(L., "to insert between") Intercalated ducts drain secretory acini in glands. In the pancreas, the duct system begins with centroacinar cells within acini then continues with intercalated, intralobular, and interlobular ducts that unite to form the main and accessory pancreatic ducts. In salivary glands (but not the pancreas), there are also striated (secretory) ducts.
Lesser omentum	In the embryo, it is the ventral mesogastrium. In the adult, it refers to the hepatogastric and hepatoduodenal ligaments.
Lesser peritoneal sac	A sac of dorsal mesogastrium that initially grows to the left and eventually drapes down over the transverse colon to form the greater omentum. Its cavity is the omental bursa.
Mesentery	Two opposing layers of visceral peritoneum anchoring the organs of the GI tract to the body wall. They contain fat and serve as a route for vessels, nerves, and lymphatics supplying the organs.

Terminology, cont'd

Mesothelium	A developmental term for the mesoderm-derived, simple squamous epithelium that lines the body cavities.
Omental bursa	The cavity of the lesser peritoneal sac.
Omental (epiploic) foramen	(G., epiploon = "omentum") Foramen of Winslow. Entry into the lesser peritoneal sac under the free edge of the lesser omentum (hepatoduodental ligament).
Omentum (lesser and greater omentum)	(L., "fat skin") The fat-filled dorsal and ventral mesenteries of the stomach. The term is not used for other mesenteries.
Omphalocele	Hernia of the midgut in the umbilical cord. The midgut intestines naturally enter the umbilical cord as they begin their tremendous growth in length. Omphalocele results if they fail to return to the abdominal cavity.
Peristalsis	(G., "around" + "constriction") Wavelike contractions of the smooth muscle wall of the intestines or other tubular structures to propel its contents. It involves the coordinated contraction of circular muscle fibers to constrict the lumen and longitudinal fibers to shorten and dilate the organ tube.
Peritoneum	Layer of simple squamous epithelium (mesothelium) with underlying connective tissue. It lines the abdominopelvic cavity. Parietal peritoneum is against the body wall; visceral peritoneum covers the mesenteries and organs.
Portal triad	Common bile duct, common hepatic artery, and hepatic portal vein located in the free edge of the lesser omentum.
Processus vaginalis	(L., "sheathlike process") A fingerlike projection of parietal peritoneum extending through the inguinal canal that pinches off to form the tunica vaginalis testis, a coelomic sac convering the testis. The proximal part usually disappears but may persist as a congenital, indirect, inguinal hernial sac.
Root of a mesentery	Where an intestinal mesentery attaches to the body wall—the site where visceral peritoneum becomes parietal peritoneum.
Scarpa's fascia	The deepest layer of the superficial body wall. Thickest in the lower abdomen, it is a membrane continuous with Colles' fascia in the scrotum.
Serous	(Pertaining to serum—L., "whey"—the clear part of any body fluid) Membranes and glands in the body are serous or mucous. Serosa (versus mucosa) are the peritoneal, pleural, and pericardial linings of the body cavities that produce a proteinaceous, watery, lubricating fluid.
Situs inversus	(L., "site" + "reversed") A left-right reversal in symmetry where the organs are in mirror-image opposite locations of their normal position. Can involve only the thorax or abdomen, or the entire body.
Superficial inguinal ring	Opening in the external oblique muscle aponeurosis through which the spermatic cord passes. Just deep to the righ the aponeurosis gives rise to the external spermatic fascia.
Zymogen	(Gr., "leaven" + "born") Zymogen granules (vesicles) in the pancreas and other glands contain the inactive precursors of their secretory enzymes.

CHAPTER 7

THE UROGENITAL SYSTEM

PRIMORDIA

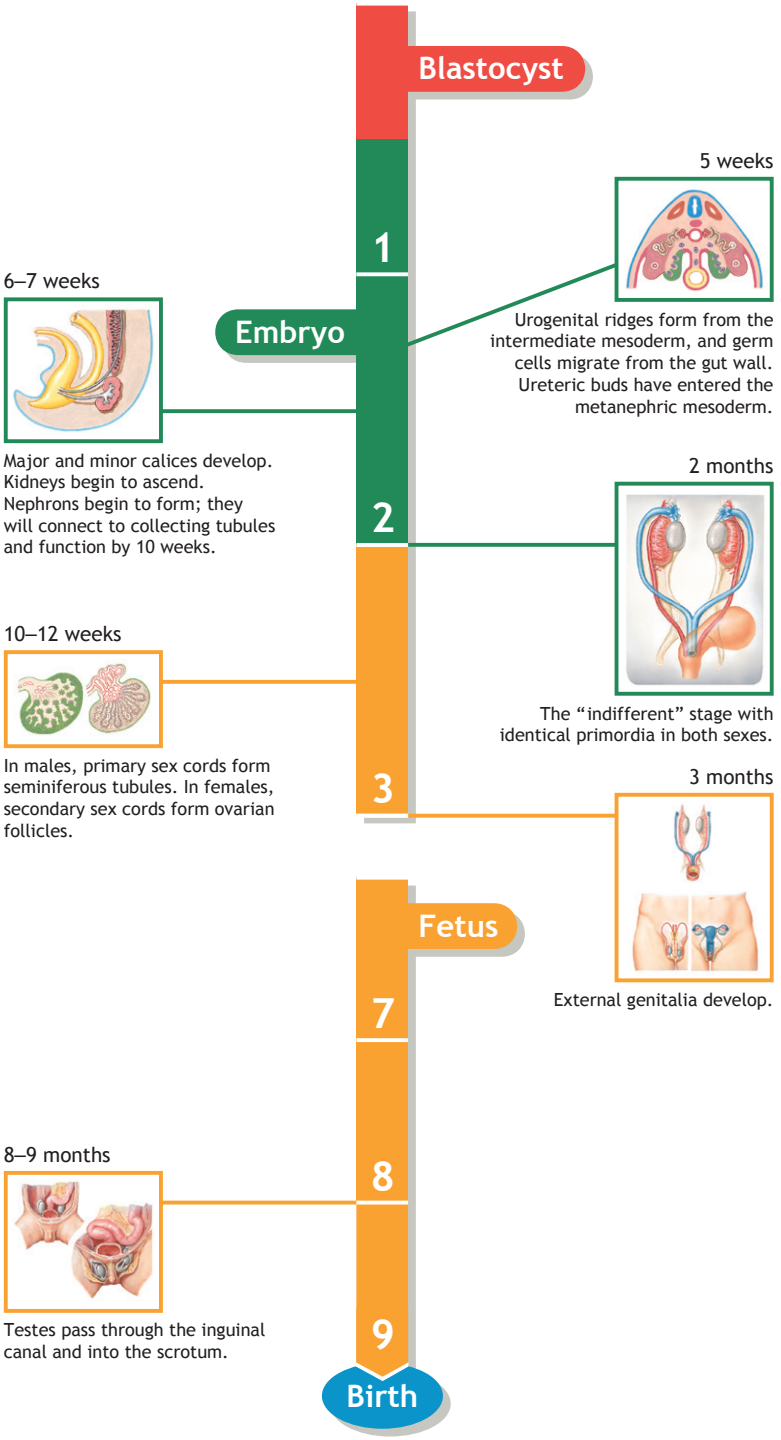
Hindgut splanchnopleure and intermediate mesoderm of the gastrula (with somatopleure contributing to the external genitalia).

PLAN

At 8 weeks, all embryos have identical primordia in the indifferent stage of urogenital development, with gonads capable of developing into testes or ovaries. Male structures disappear in embryos destined to become females, and the female primordia disappear as male development proceeds. The kidneys develop from the intermediate mesoderm in three successive waves, from cranial to caudal, with the third, most inferior pair of kidneys (metanephros) becoming the permanent kidneys. Complicating factors are the relatively huge size of the middle, mesonephric kidney (the first functioning kidney), and the change in function of the mesonephric duct in the male from urinary (a temporary ureter) to genital (the ductus deferens and related structures).

TIMELINE

Prenatal Time Scale (Months)



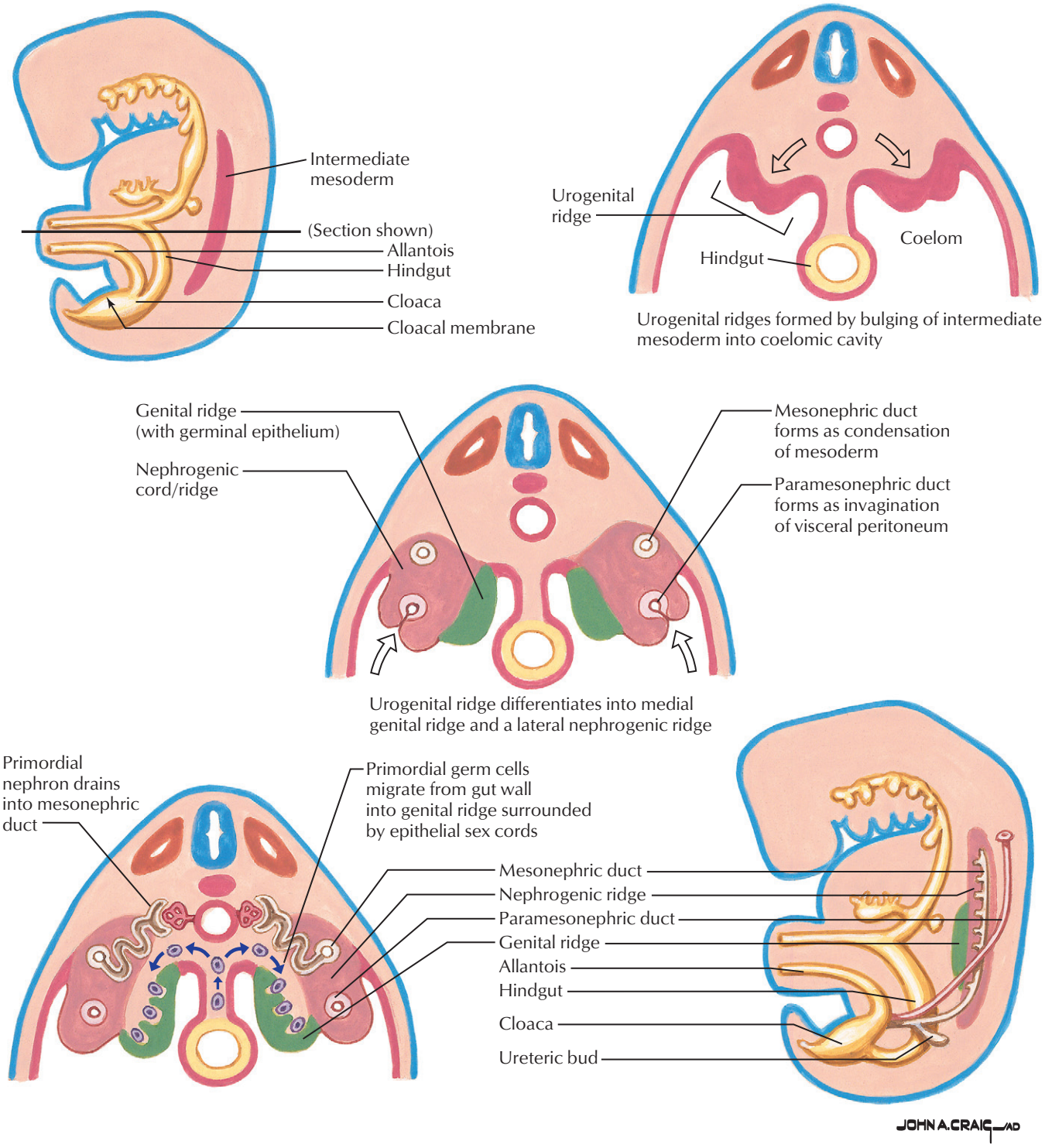
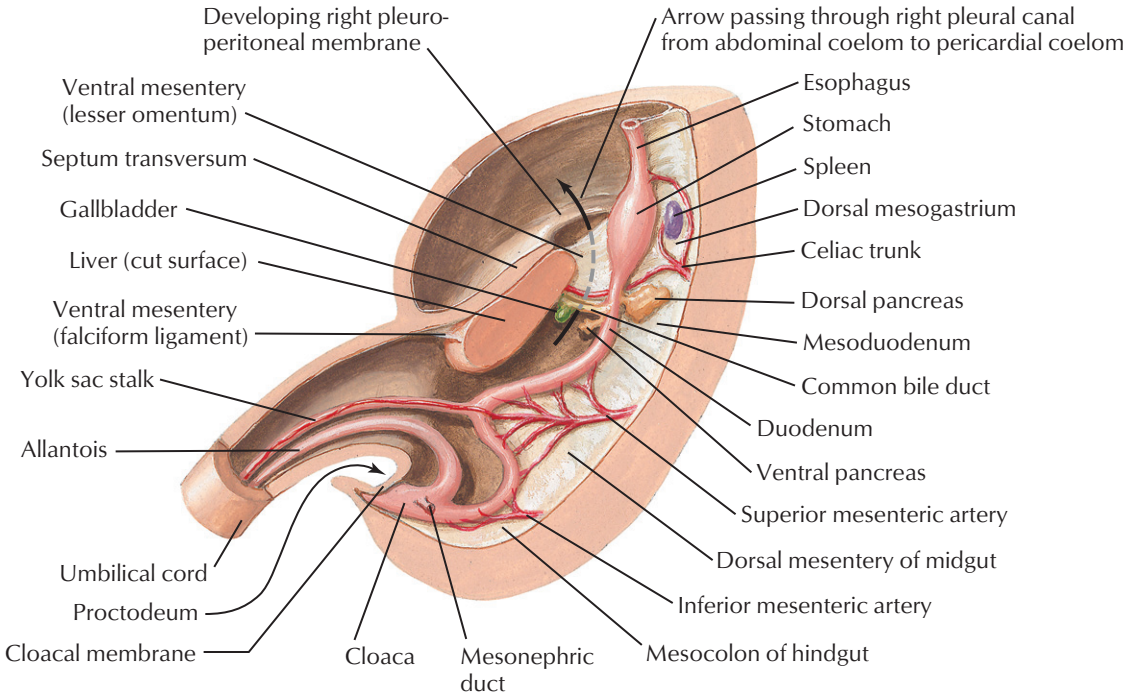


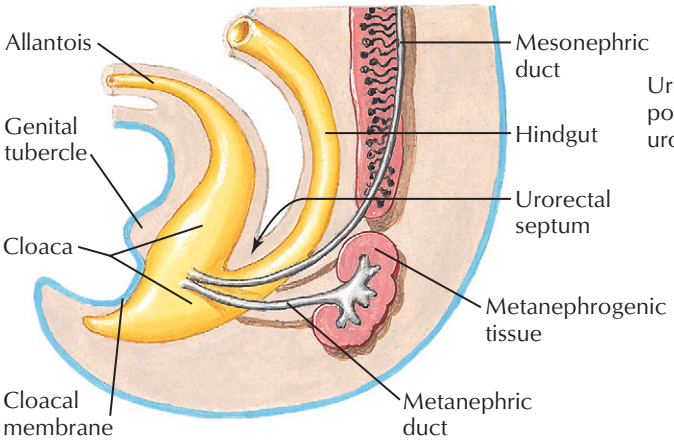
FIGURE 7.1 EARLY PRIMORDIA

The caudal end of the **hindgut** has a dilated chamber, the **cloaca.** Its endoderm is in tight contact with the surface ectoderm, and together they form the **cloacal membrane.** Extending from the cloaca into the umbilical cord is the **allantois.** The intermediate mesoderm of the gastrula bulges into the dorsal aspect of the intraembryonic coelom as a **urogenital ridge** on each side. It develops into two ridges: a medial **genital (gonadal) ridge** and a lateral **nephrogenic ridge** or **cord.** Primordial germ cells begin to migrate from the endoderm of the hindgut toward the genital ridge through the dorsal mesentery. A **mesonephric (wolffian) duct** and **paramesonephric (müllerian) duct** form in the nephrogenic ridge (cord).

Abdominal foregut, midgut, and hindgut at 5 weeks



Division of the cloaca by the urorectal septum



Urogenital sinus and rectum

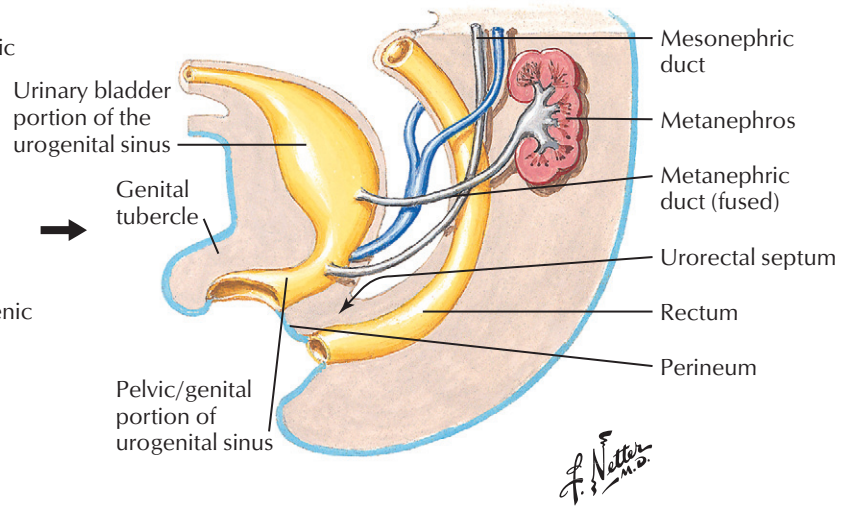


FIGURE 7.2 DIVISION OF THE CLOACA

The **urorectal septum** between the allantois and hindgut divides the cloaca in the frontal plane into an anterior **urogenital sinus** and posterior **rectum.** The septum divides the cloacal membrane into a urogenital membrane and anal membrane. The upper part of the urogenital (UG) sinus is the fusiform urinary bladder. The lower pelvic and phallic parts of the UG sinus (UG sinus proper) form the urethra and related glands and structures in each sex. The genital portion of the urogenital sinus is closely related to the **genital tubercle,** a swelling of somatopleure. The metanephric duct (future ureter) opens into the developing urinary bladder; the male (mesonephric) and female (paramesonephric) genital ducts shift to a more caudal position on the UG sinus.

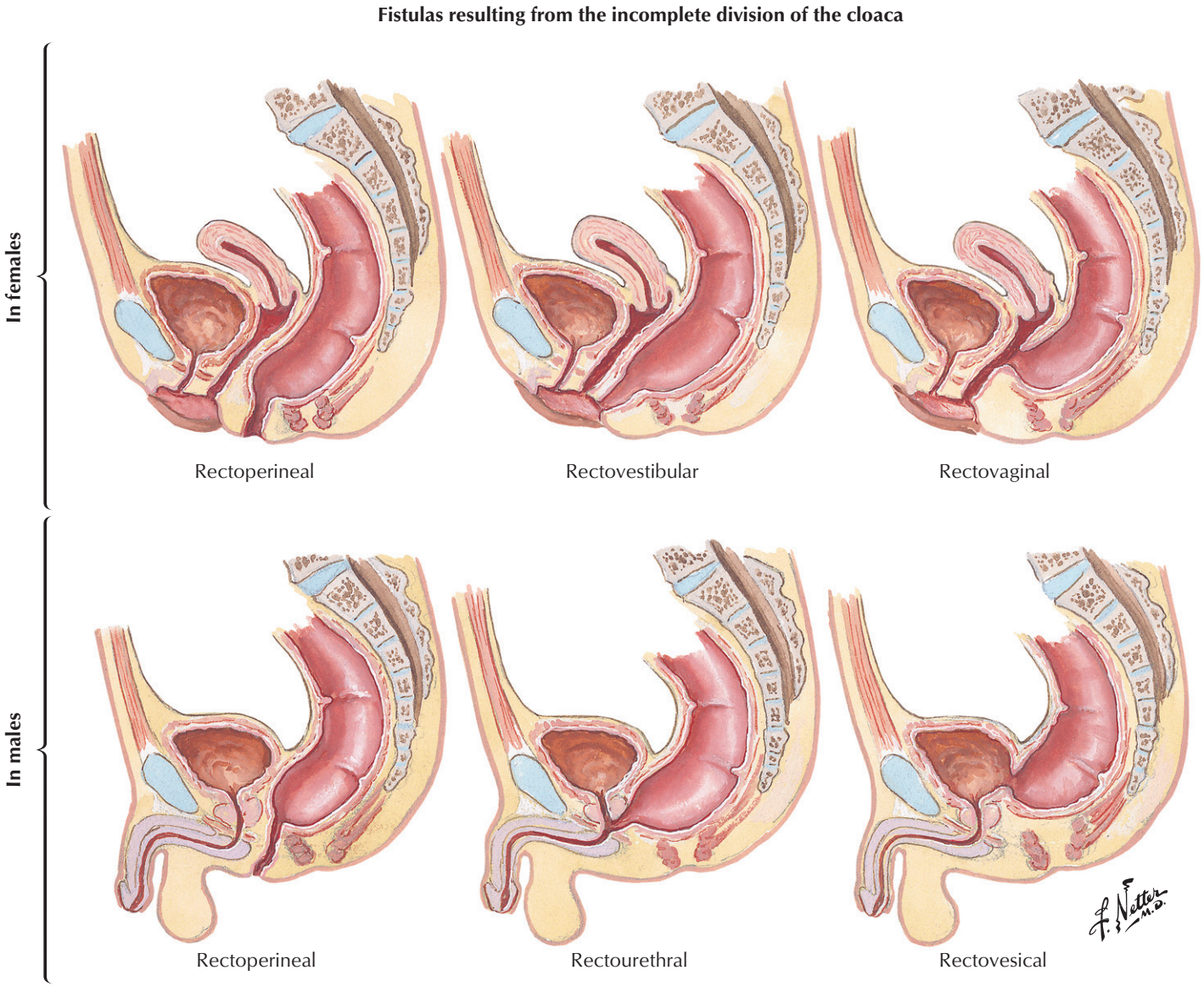


FIGURE 7.3 CONGENITAL CLOACAL ANOMALIES

If the urorectal septum does not completely divide the cloaca, the rectum will connect anteriorly with urinary or genital structures derived from the urogenital sinus. The resulting fistulas are all associated with an imperforate anus. A rectoperineal fistula opens to the surface, but it is an abnormal connection anterior to the external anal sphincter (and anus) through the central tendon of the perineum (perineal body).

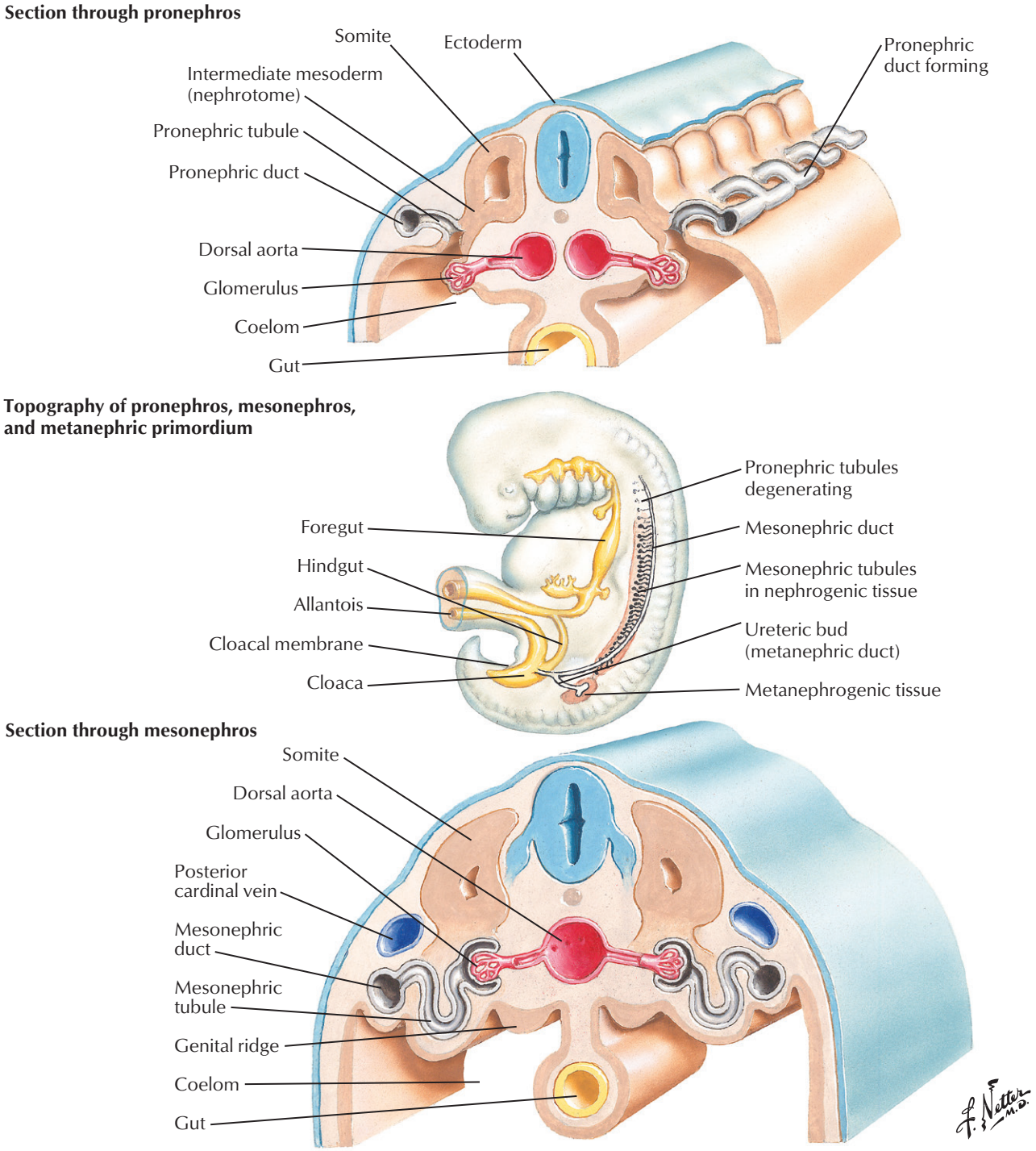
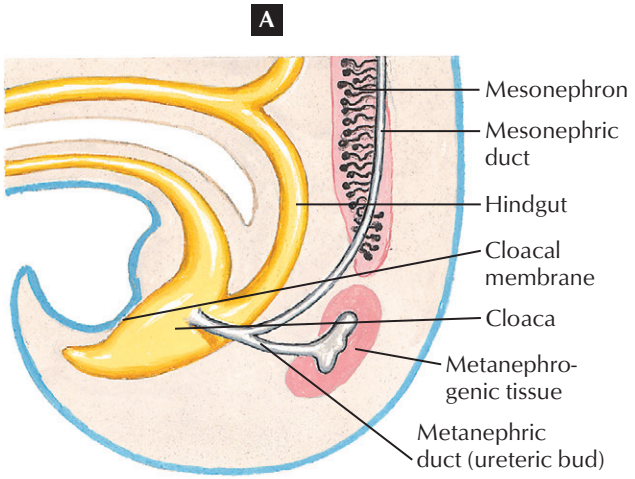


FIGURE 7.4 PRONEPHROS, MESONEPHROS, AND METANEPHROS

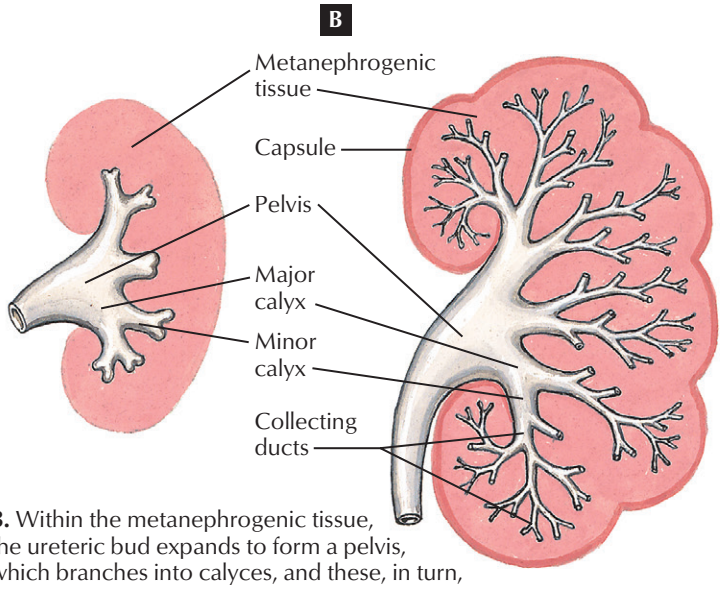
The intermediate mesoderm differentiates into nephrogenic tissue in the nephrogenic ridge lateral to the genital ridge. From cranial to caudal it forms three successive kidneys.

- The **pronephros** never fully develops and quickly diminishes.
- The **mesonephros** is the first functioning kidney, with glomeruli, **mesonephric tubules,** and a **mesonephric duct** that drains embryonic urine into the dividing cloaca.
- The **metanephros** becomes the permanent kidney.

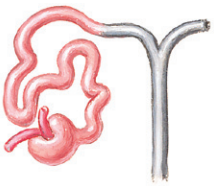
The **metanephric duct** (future ureter) develops from a **ureteric bud** that grows from the caudal end of the mesonephric duct into the metanephric mesoderm. It quickly shifts inferiorly to make its own connection with the cloaca/urogenital sinus/bladder.



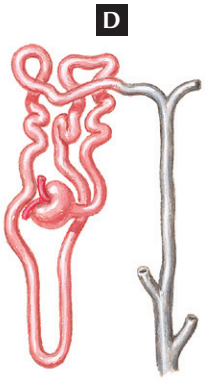
A. The metanephric duct (ureteric bud) has grown out from the mesonephric duct, close to termination of the latter in cloaca, and has invaded the metanephrogenic mesoderm.



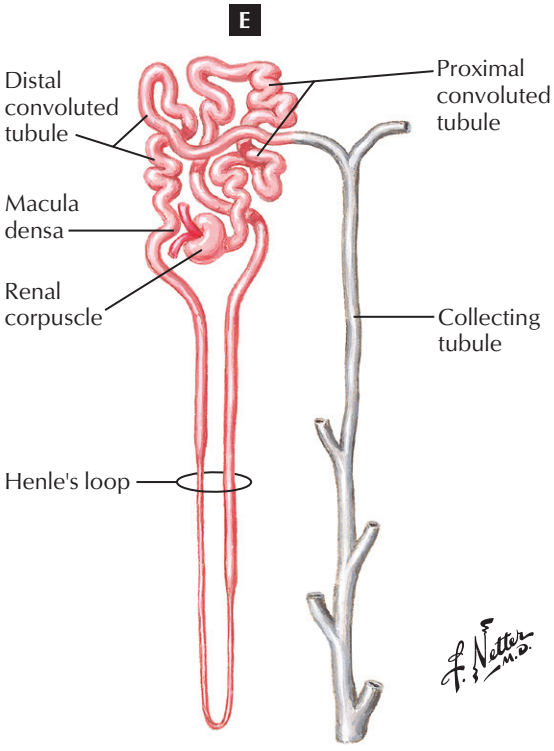
B. Within the metanephrogenic tissue, the ureteric bud expands to form a pelvis, which branches into calyces, and these, in turn, bud into successive generations of collecting ducts.



C. The distal ends of the collecting ducts connect with the tubule system of the nephron developing from the metanephric mesoderm. The nephron extends from the collecting duct to the renal corpuscle.



D. The tubule lengthens, coils, and begins to dip down toward the renal pelvis, as Henle's loop; one area of the tubule remains close to the glomerular mouth, as the future macula densa.



E. The loop elongates; renal corpuscle, proximal tubule, Henle's loop, distal tubule, and macula densa of mature nephron are thus derived from metanephrogenic mesoderm and collecting tubules from the metanephric duct.

FIGURE 7.5 DEVELOPMENT OF THE METANEPHROS

The metanephric kidneys become the permanent kidneys. Each kidney develops from two primordia: a **ureteric bud** from a mesonephric duct that grows into the **metanephric mesoderm** at the caudal end of the intermediate mesoderm of the gastrula. The ureteric bud (metanephric duct) soon makes its own connection to the urinary bladder. The ureter, renal pelvis, calyces, and collecting ducts of each kidney develop from the ureteric bud. The tubule system of the nephron (proximal and distal convoluted tubules, Henle's loop, and Bowman's capsule of the renal corpuscle) develops from the metanephric mesoderm.

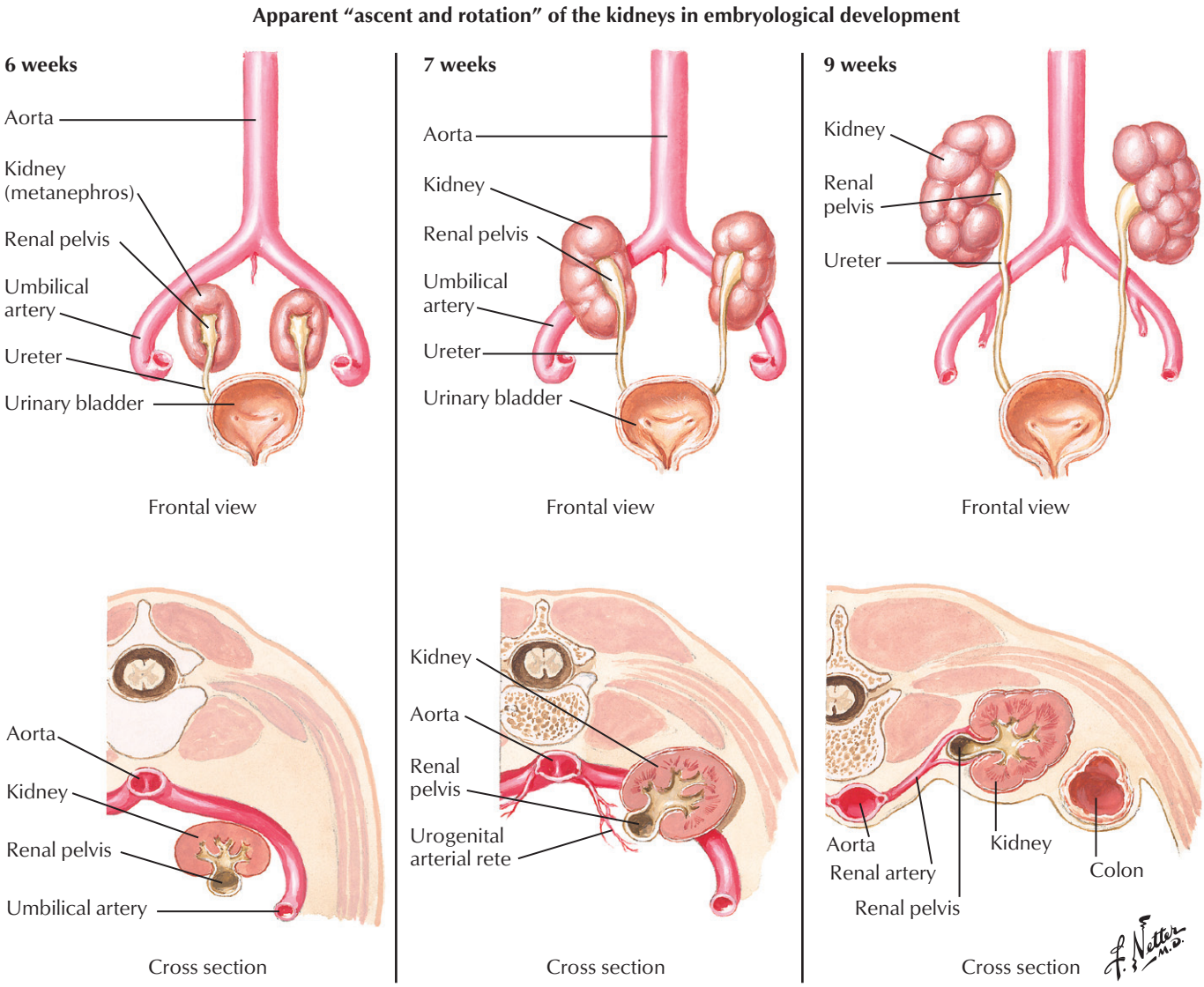


FIGURE 7.6 ASCENT AND ROTATION OF THE METANEPHRIC KIDNEYS

After week 8, the mesonephric mesoderm begins to disappear. In females, the mesonephric (wolffian) duct disappears; in males, it connects to the developing testis as the ductus (vas) deferens. The metanephric, permanent kidney is in the pelvis at the caudal end of the intermediate mesoderm. It ascends to the posterior wall of the abdomen. The renal hilum of the metanephric kidneys faces anteriorly in the pelvis; the smooth, convex surface is posterior. As the kidneys ascend to the posterior abdominal wall, each rotates 90 degrees so that the renal pelvis and blood vessels in the hilum are medial as in the adult. The kidneys are in a retroperitoneal location during the entire process.

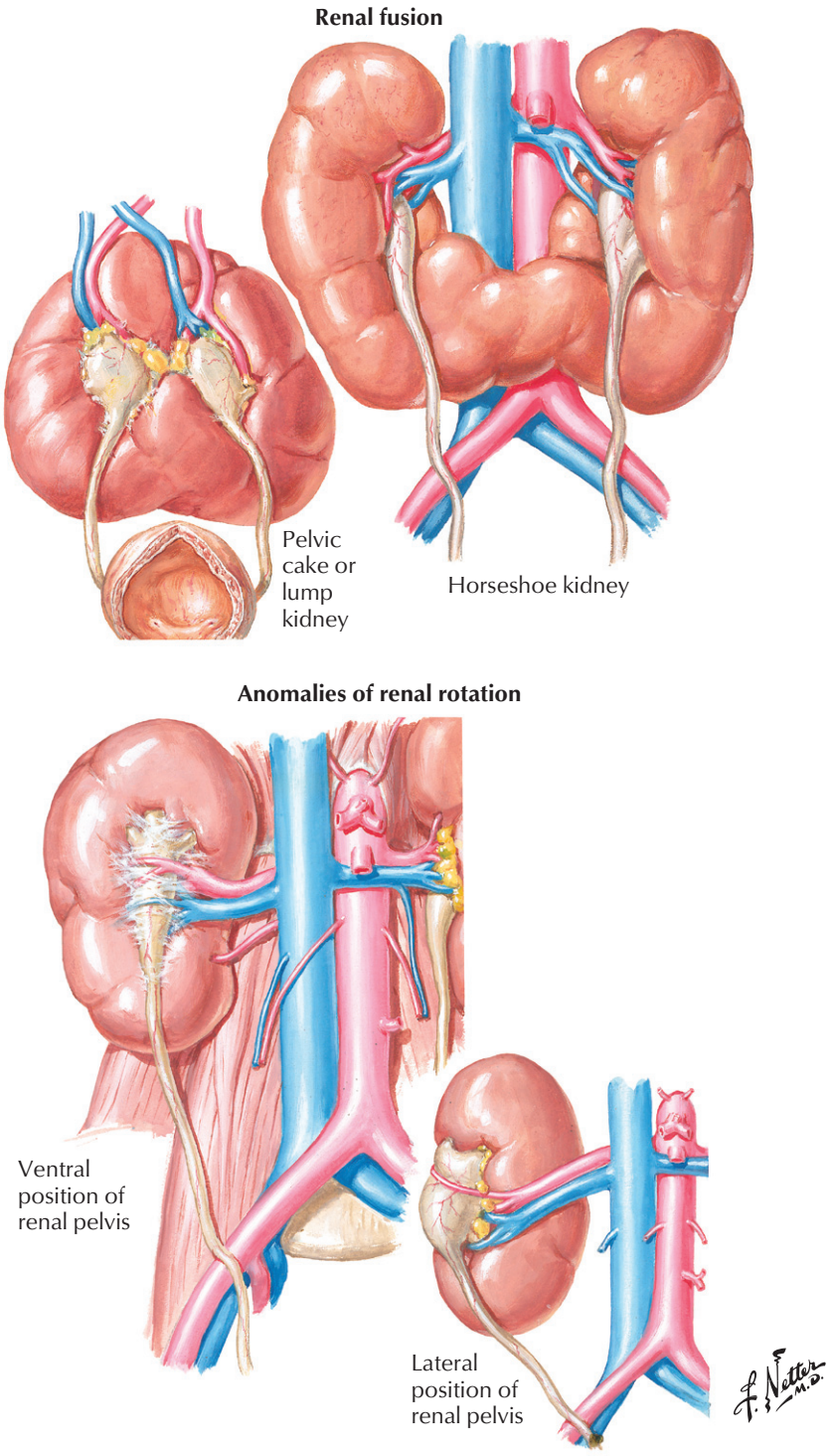


FIGURE 7.7 KIDNEY ROTATION ANOMALIES AND RENAL FUSION

Anomalies include failure of the metanephric kidneys to ascend, failure to rotate, excessive rotation, and rotation in the opposite direction. The ureteric buds may also fuse in the pelvis. If a fused kidney ascends, it encounters the inferior mesenteric artery (not shown) and assumes the shape of a horseshoe as it extends around it.

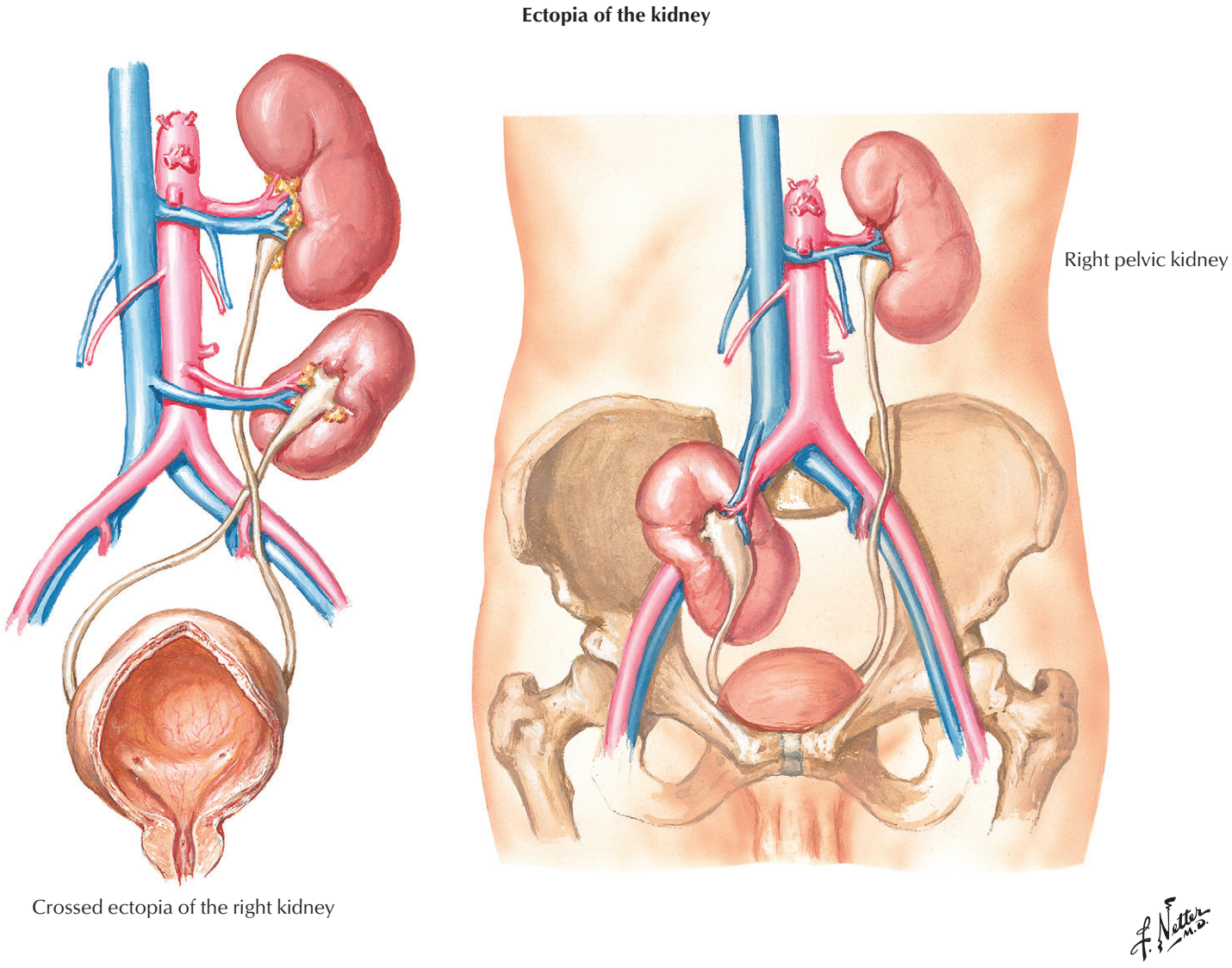


FIGURE 7.8 KIDNEY MIGRATION ANOMALIES AND BLOOD VESSEL FORMATION

A kidney can fail to ascend on one side only, or a kidney can migrate to the opposite side of the body. The development of renal blood vessels is unique. Most organs "trail" their blood supply as they migrate. As the kidneys ascend, new blood vessels form at higher levels of the aorta and inferior vena cava and connect to the kidneys as lower vessels disappear. Renal arteries of pelvic kidneys originate near the bifurcation of the aorta. For normal adult kidneys, they are at the level of the superior mesenteric arteries of the midgut. Sometimes, more inferior renal vessels fail to disappear. This is the embryonic basis of multiple renal arteries and veins in the adult.

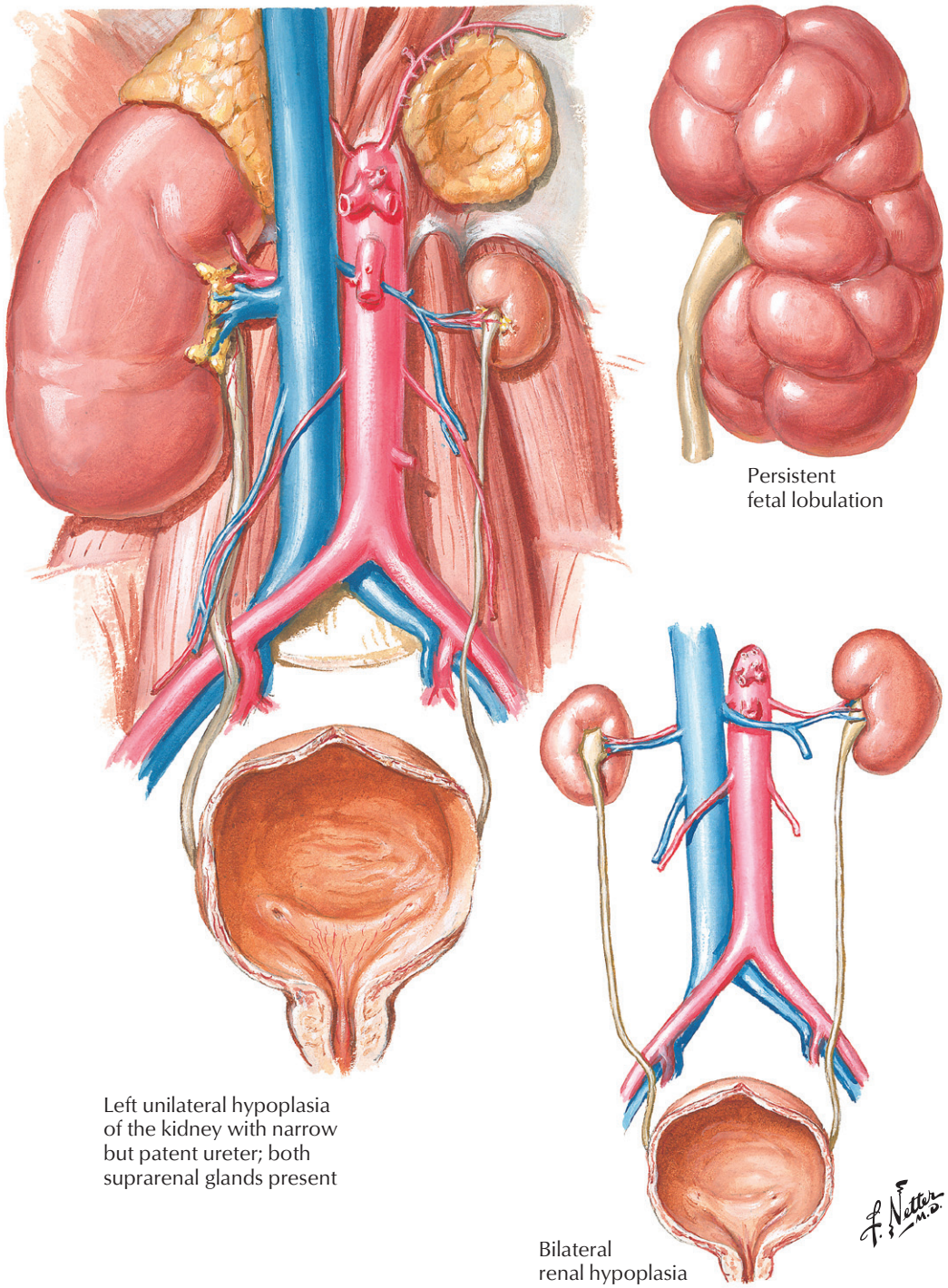


FIGURE 7.9 HYPOPLASIA

A kidney may be underdeveloped (hypoplasia) or completely absent (agenesis), and either condition may be unilateral or bilateral. Development of the suprarenal (adrenal) glands is unrelated to the development of the kidneys. The suprarenal glands are usually normal in size and location if the kidneys are ectopic or hypoplastic. Another kidney abnormality is persistent fetal lobulation. Fetal kidneys do not have the smooth surface of adult kidneys.

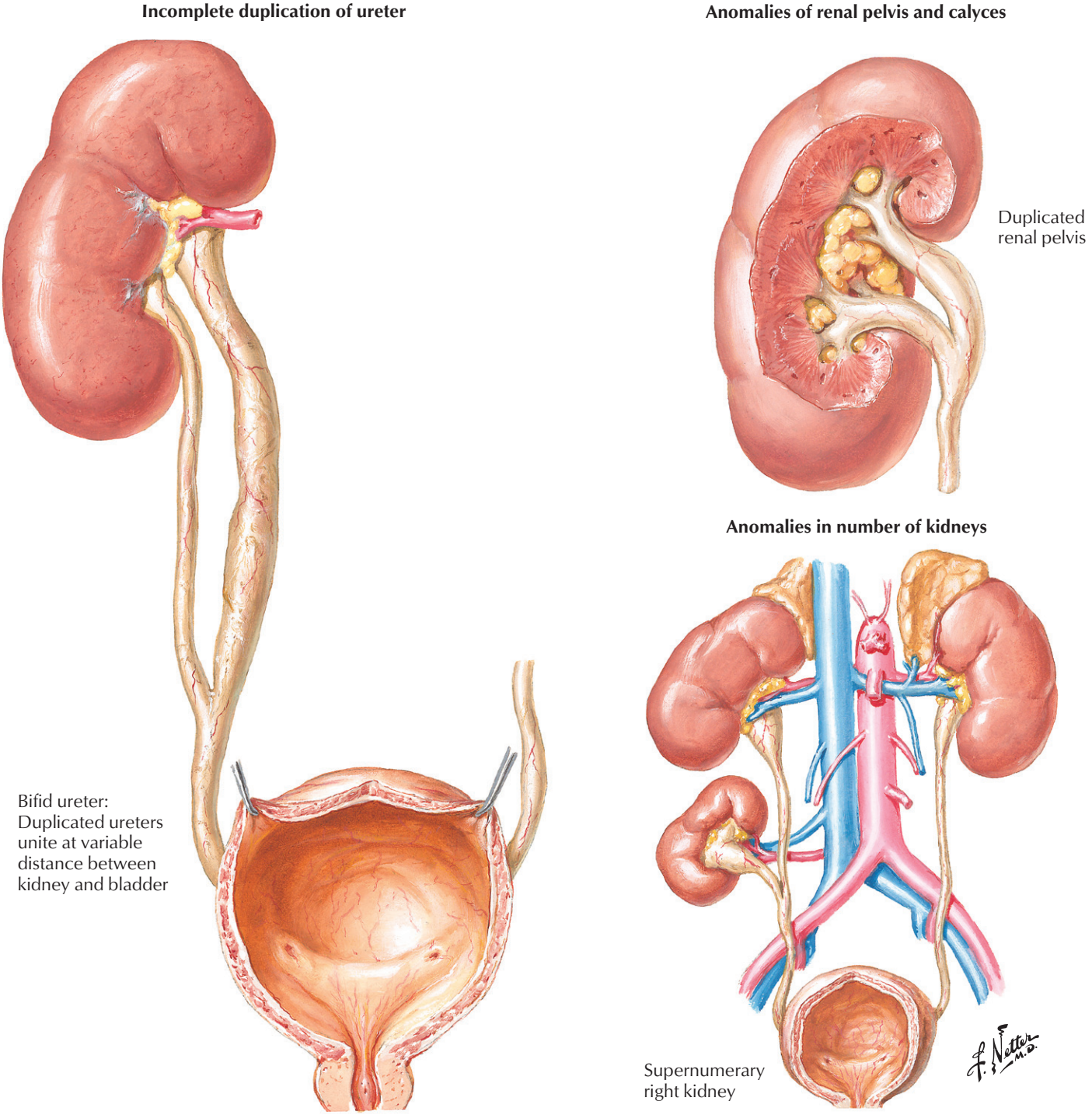
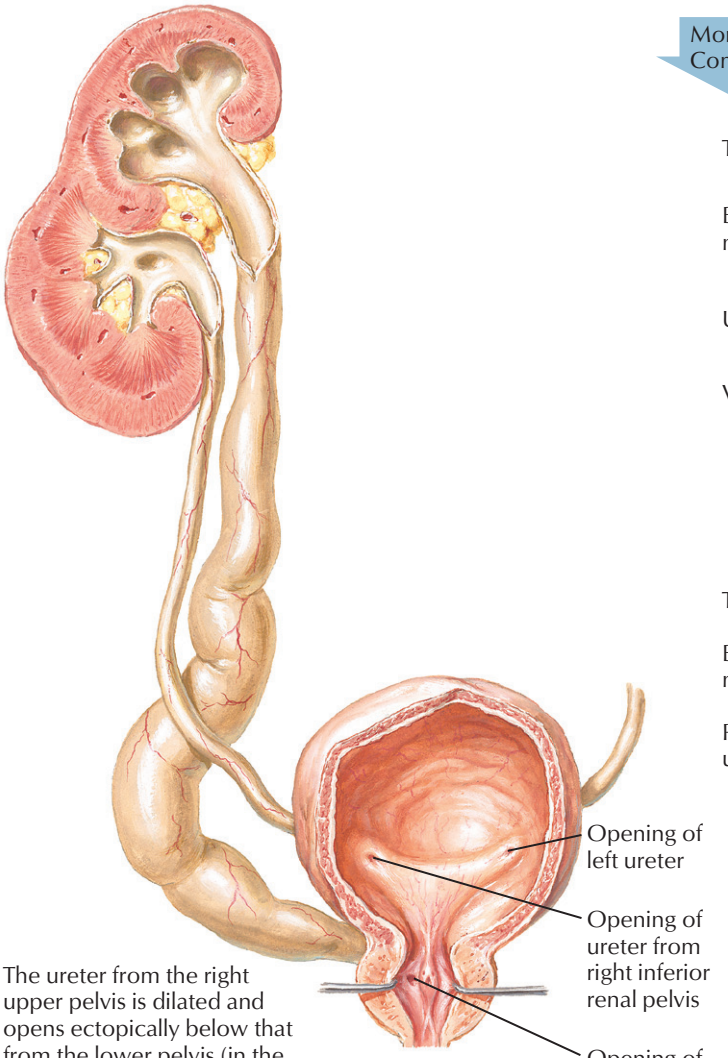


FIGURE 7.10 URETERIC BUD DUPLICATION

The effects of division of the ureteric bud range from bifurcation of the renal pelvis or ureter to complete duplication of the ureter and kidney. The greater the extent of division of the ureteric bud, the more likely the metanephric mesoderm will also divide and form two kidneys. Like most of the other anomalies, duplication can be unilateral or bilateral.

Complete duplication of the ureter



The ureter from the right upper pelvis is dilated and opens ectopically below that from the lower pelvis (in the prostatic urethra) according to the Weigert-Meyer law

Observed sites of ectopic ureteral orifices

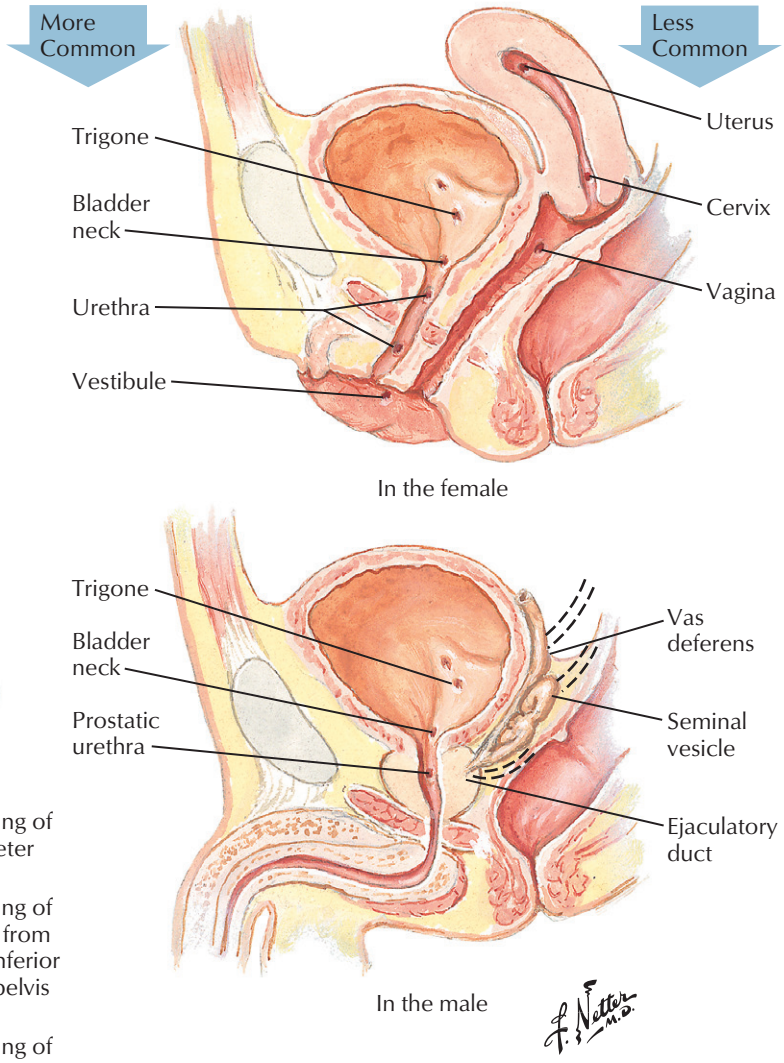


FIGURE 7.11 ECTOPIC URETERS

The ureteric buds originate from the mesonephric duct instead of the cloaca, and this is often the embryonic basis for the ectopic location of the distal ureter in pelvic organs. The mesonephric duct migrates to a lower position on the urogenital sinus in both sexes before it disappears in the female and becomes the vas deferens in the male. The ureters can be carried with it to open on the urethra, prostate, vestibule, or other structures inferior to the bladder.

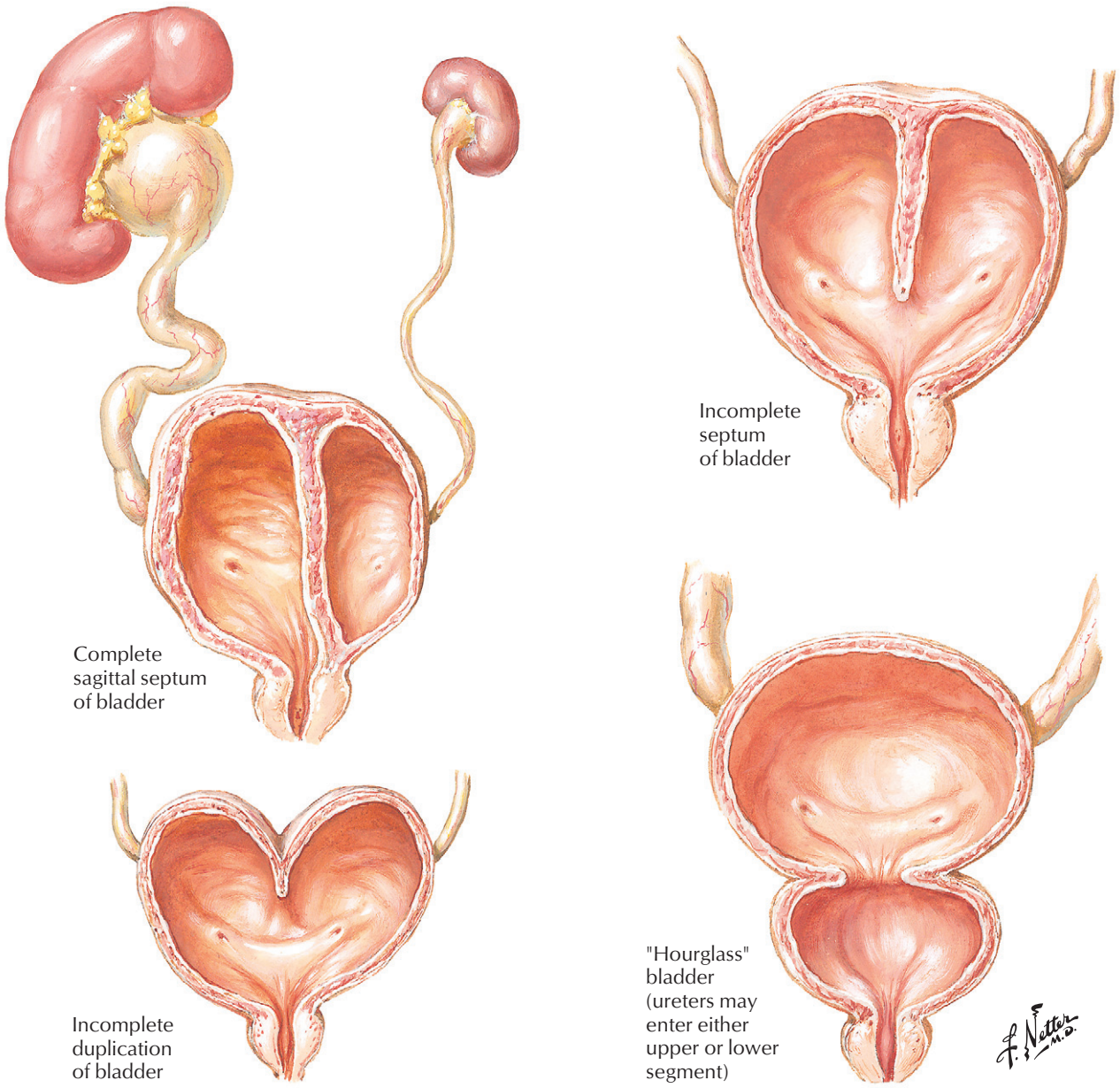


FIGURE 7.12 BLADDER ANOMALIES

The urinary bladder separates from the rectum when the urorectal septum divides the cloaca in a coronal plane between the allantois and hindgut. Partial or complete septa in a sagittal plane within the urinary bladder are unrelated to this process. They usually result from duplication of the cloaca, and the rectum and part of the colon are often affected as well. The mechanisms for other types of division or constriction of the bladder are not as well understood.

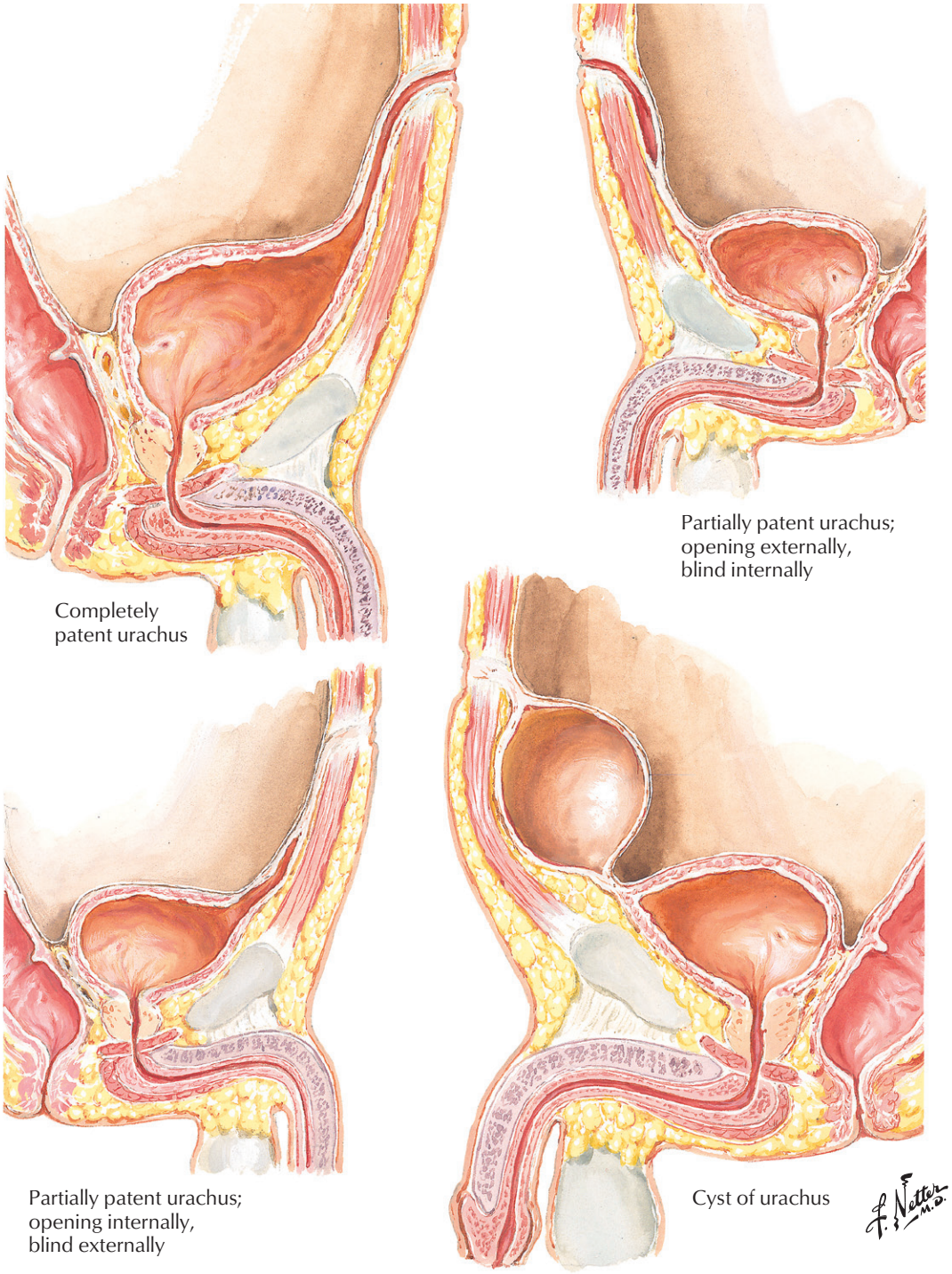
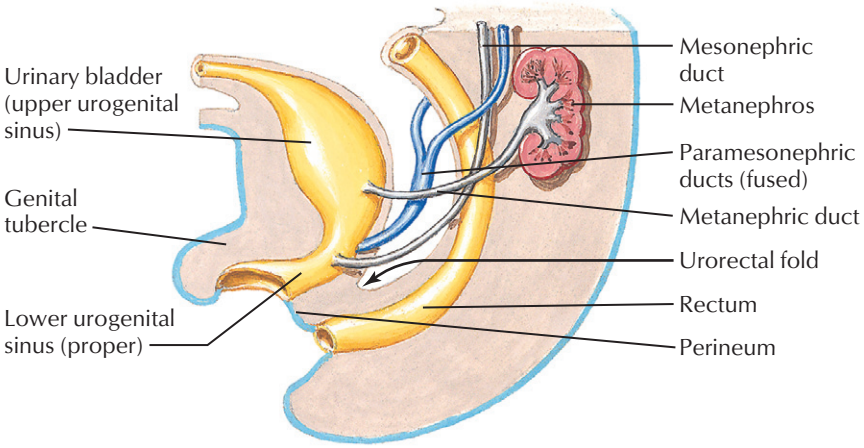
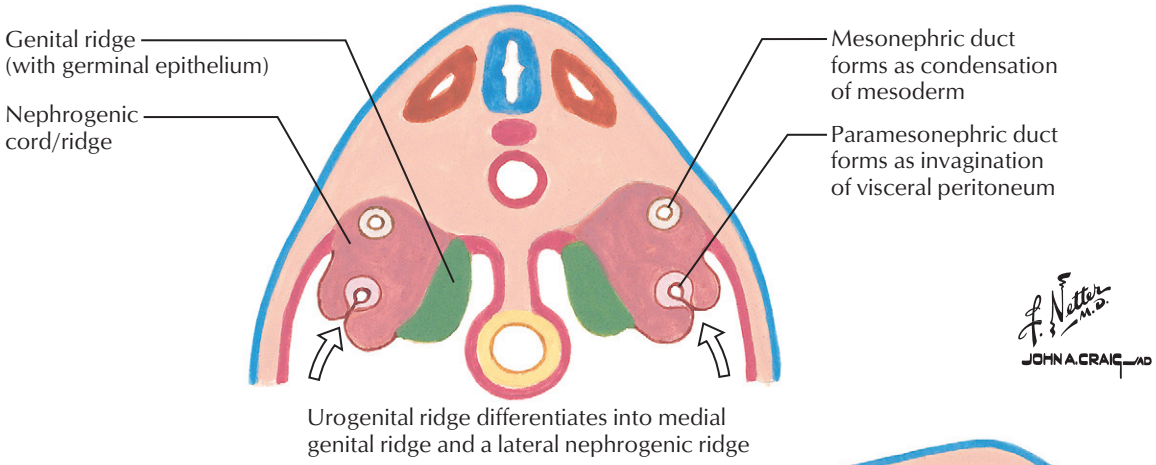


FIGURE 7.13 ALLANTOIS/URACHUS ANOMALIES

The **urachus** is the fibrous remnant of the **allantois,** an extension of the cloaca/urogenital sinus into the umbilical cord. The lumen of the allantois may persist as a **fistula** (completely patent lumen), **sinus** (blind pit at either end), or **cyst** (enclosed swelling). These types of congenital defects may occur in any tubular primordium in the embryo that is supposed to form a fibrous cord or disappear.

The metanephric duct (ureter) opens into the urinary bladder (upper UG sinus). The paramesonephric (müllerian) ducts fuse in the midline inferiorly and connect to the lower urogenital sinus along with the mesonephric (wolffian) ducts.





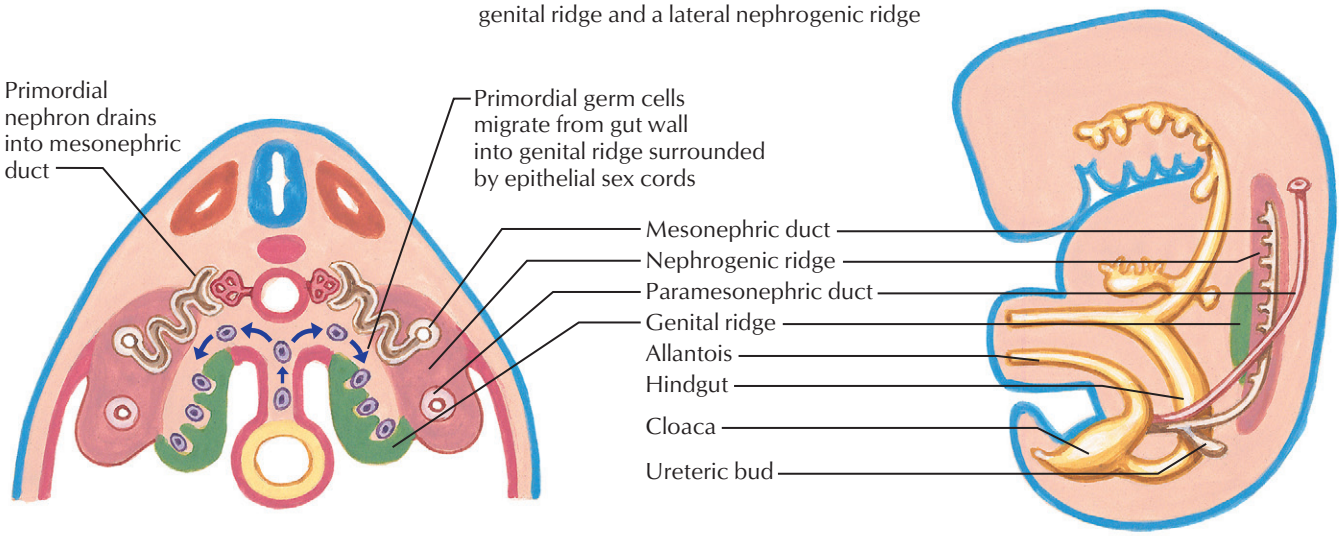
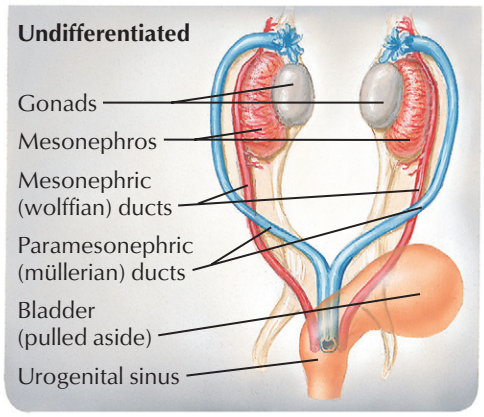


FIGURE 7.14 PRIMORDIA OF THE GENITAL SYSTEM

The genital primordia include the **genital tubercle** of somatopleure associated with the lower portion of the **urogenital sinus** and the **gonad** developing from the **genital ridge** of intermediate mesoderm. The **paramesonephric duct** develops beside the **mesonephric duct** by an invagination of the peritoneum. The gonads are closely applied to the mesonephric kidneys, a relationship that is very important in the male. When the mesonephric kidneys disappear, the mesonephric duct and tubules connect with the developing testis and change their function from urinary (mesonephric ureter) to genital (ductus deferens, seminal vesicle, ejaculatory duct, and related structures).

Anterior view (mesonephros will disappear in both sexes)



Lateral view (both sexes have identical primordia)

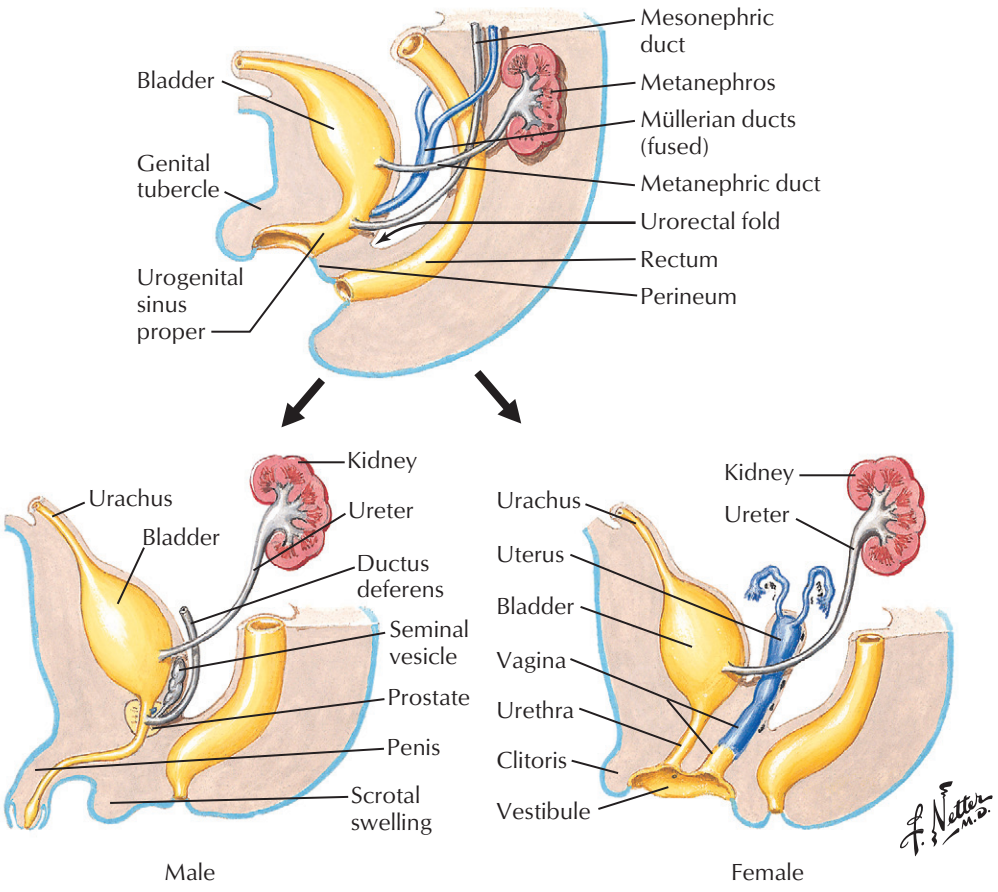


FIGURE 7.15 8-WEEK UNDIFFERENTIATED (INDIFFERENT) STAGE

Males and females have the same primordia in the undifferentiated stage at the end of the embryonic period (8 weeks). In males, the paramesonephric ducts degenerate. The mesonephric ducts become the ductus deferens, ejaculatory ducts, and seminal vesicles. The urogenital sinus develops into the urinary bladder, prostate gland, bulbourethral (Cowper's) and paraurethral glands, and prostatic, membranous, and penile (spongy) urethra. In females, the mesonephric ducts degenerate, and the paramesonephric ducts develop into the uterine tubes, uterus, and upper part of the vagina. The urogenital sinus forms the bladder, urethra, greater vestibular and paraurethral glands, vestibule, and lower part of the vagina. The allantois becomes the fibrous urachus in both sexes.

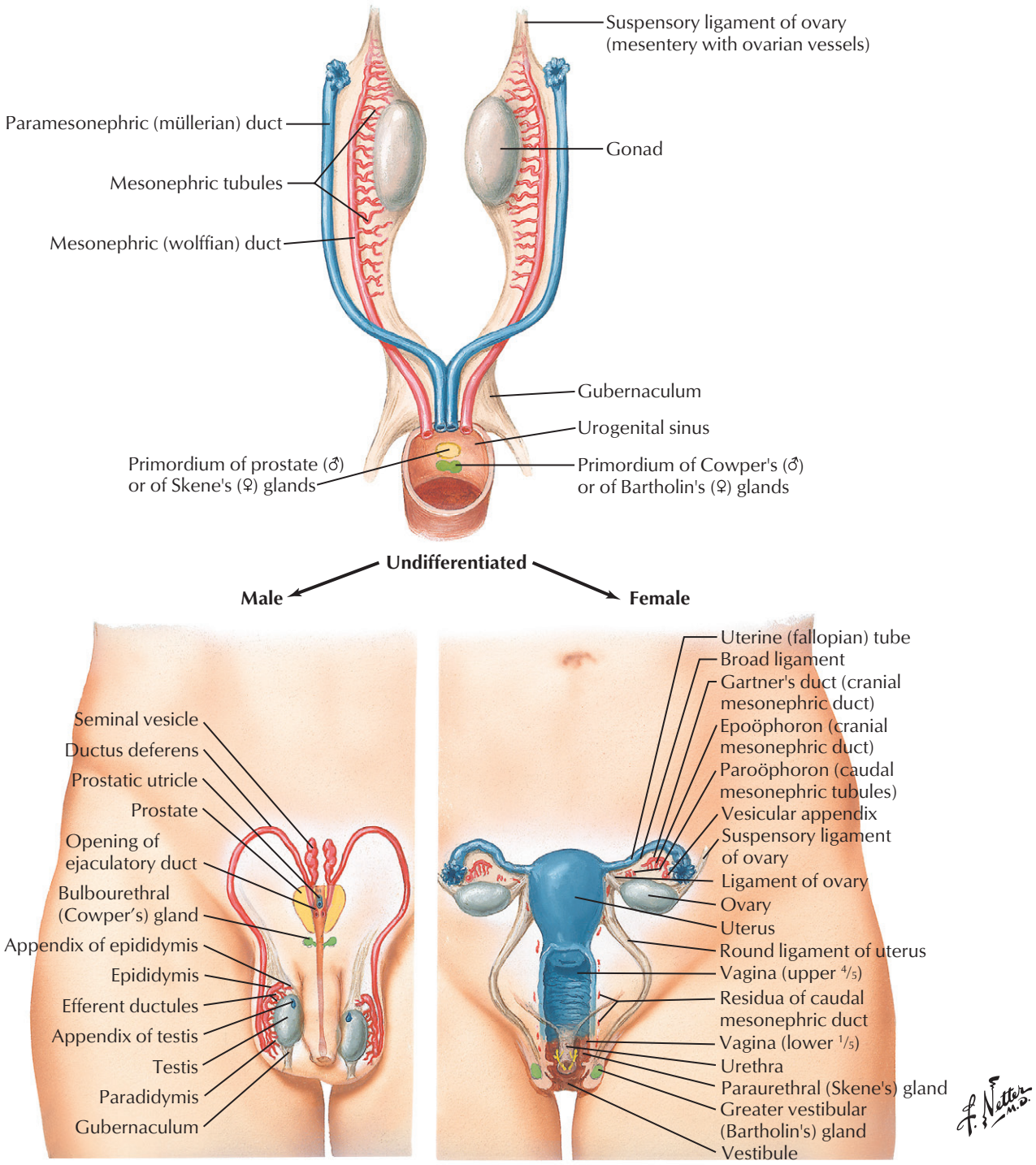


FIGURE 7.16 ANTERIOR VIEW OF THE DERIVATIVES

The genetic sex of the embryo determines the sexual path of differentiation. The **sex regulatory (SRY) gene** on the Y chromosome codes for a **testis-determining factor (TDF)** that causes the gonad to become a testis. Testosterone secreted by Leydig cells in the testis during week 9 causes external genital development and the mesonephric ducts to develop into the male genital duct system. The glycoprotein **antimüllerian hormone (AMH)** causes the degeneration of the paramesonephric ducts and promotes growth of the mesonephric ducts. Female development is the "default" system. The absence of testosterone and AMH in the female causes the mesonephric ducts to regress and the paramesonephric ducts to develop into the female genital structures.

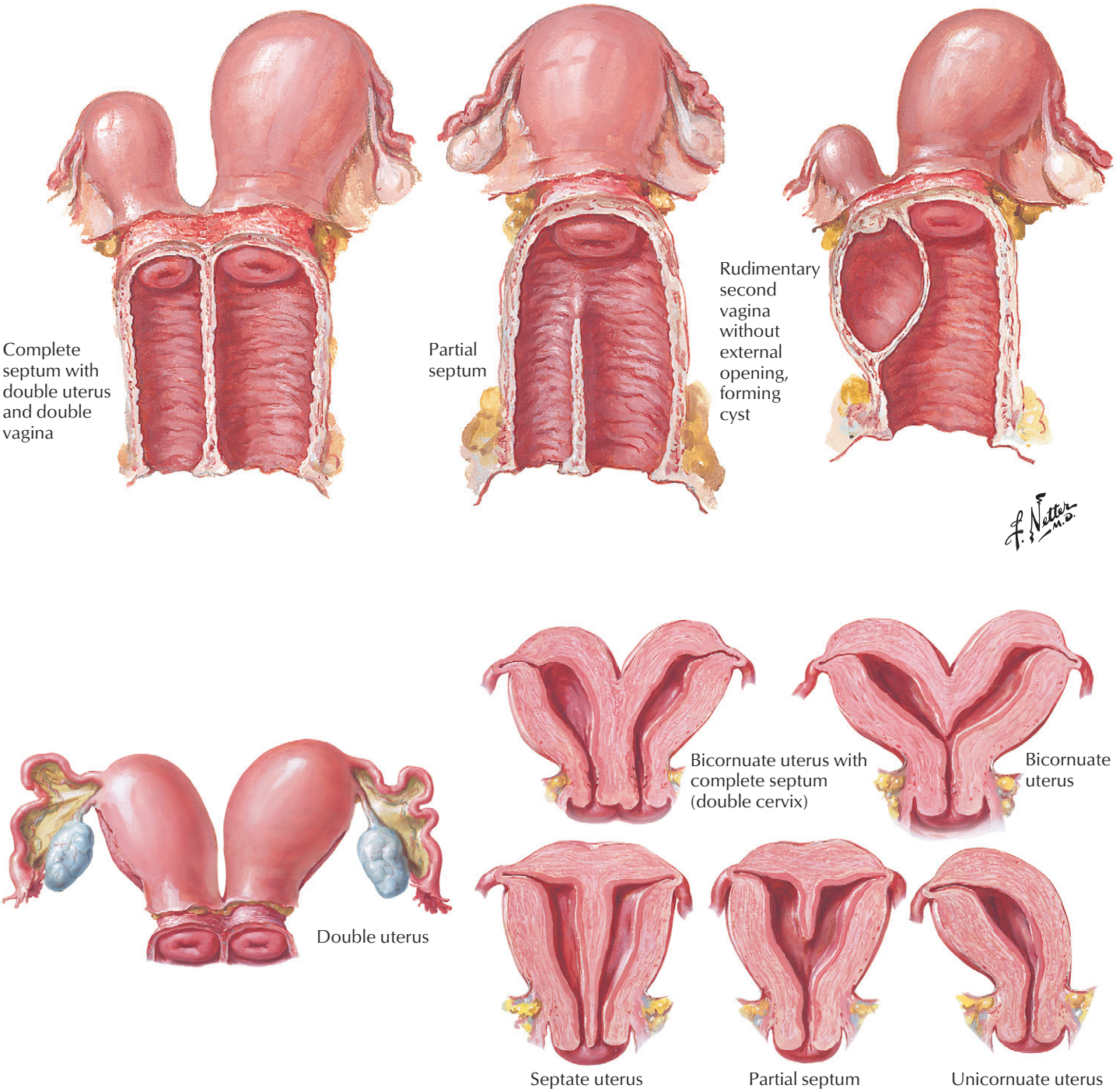


FIGURE 7.17 PARAMESONEPHRIC DUCT ANOMALIES

The left and right paramesonephric (müllerian) ducts fuse in the midline as they connect with the urogenital sinus. Anomalies of the uterus, uterine tubes, and upper vagina result from the absence of one duct, complete absence of fusion, or varying degrees of fusion of the left and right ducts. The lower part of the vagina can also be affected. It develops from **sinovaginal bulbs** that are endodermal extensions of the urogenital sinus. An epithelial **vaginal plate** occludes the lumen of the vaginal primordium. It becomes hollow, except for a membranous **hymen** that separates the vaginal lumen from the vestibule.

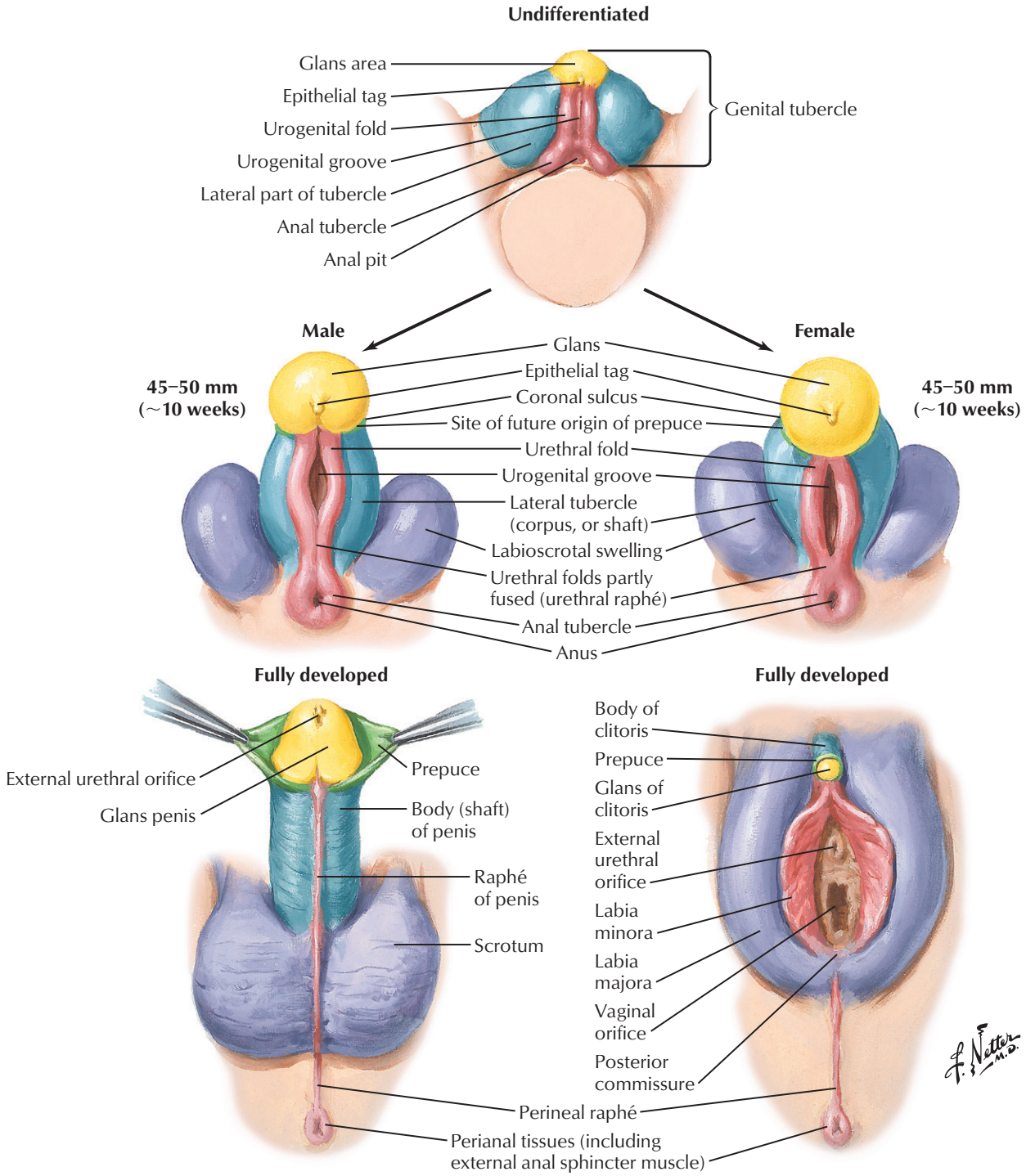


FIGURE 7.18 HOMOLOGUES OF THE EXTERNAL GENITAL ORGANS

The earliest primordium for the external genital organs is the **genital tubercle,** a swelling of somatopleure dorsal to the caudal end of the urogenital (UG) sinus. **UG folds** flank the external genital part of the UG sinus, and **labioscrotal folds** of somatopleure appear lateral to the UG folds. The genital tubercle forms the penis and clitoris. The UG folds become the labia minora, and the labioscrotal folds become the labia majora and scrotum. The UG sinus develops into the vestibule and urethra in the female (and related glands). In the male, it folds within the genital tubercle to become most of the penile urethra (except the navicular fossa in the glans). The UG folds in the male may contribute a bit to the ventral surface of the penis.

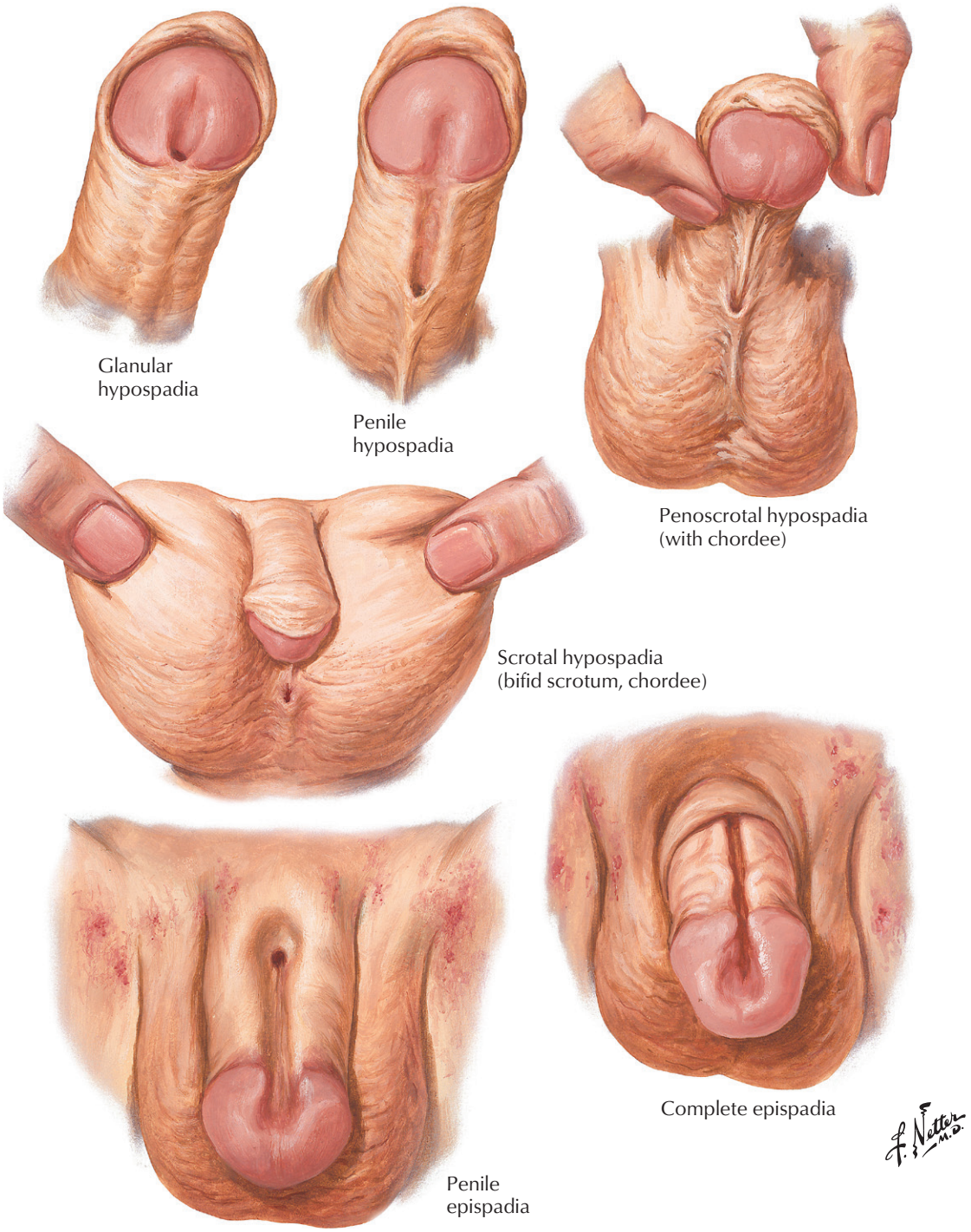


FIGURE 7.19 HYPOSPADIAS AND EPISPADIAS

The penile urethra is formed by two mechanisms. Most of the penile urethra develops as the urogenital (UG) folds fuse on the ventral surface of the penis to enclose the distal UG sinus as the penile (spongy) urethra. The ectoderm at the tip of the glans penis invaginates as a cord that connects to the end of the spongy urethra, then becomes hollow to form the navicular fossa. Hypospadias results from failure of fusion of the UG folds to varying degrees caused by insufficient production of androgens from the fetal testes or lack of hormone receptors. Epispadias results from the improper location of the genital tubercle relative to the UG sinus, and the UG membrane breaks open on its dorsal surface instead of on the ventral.

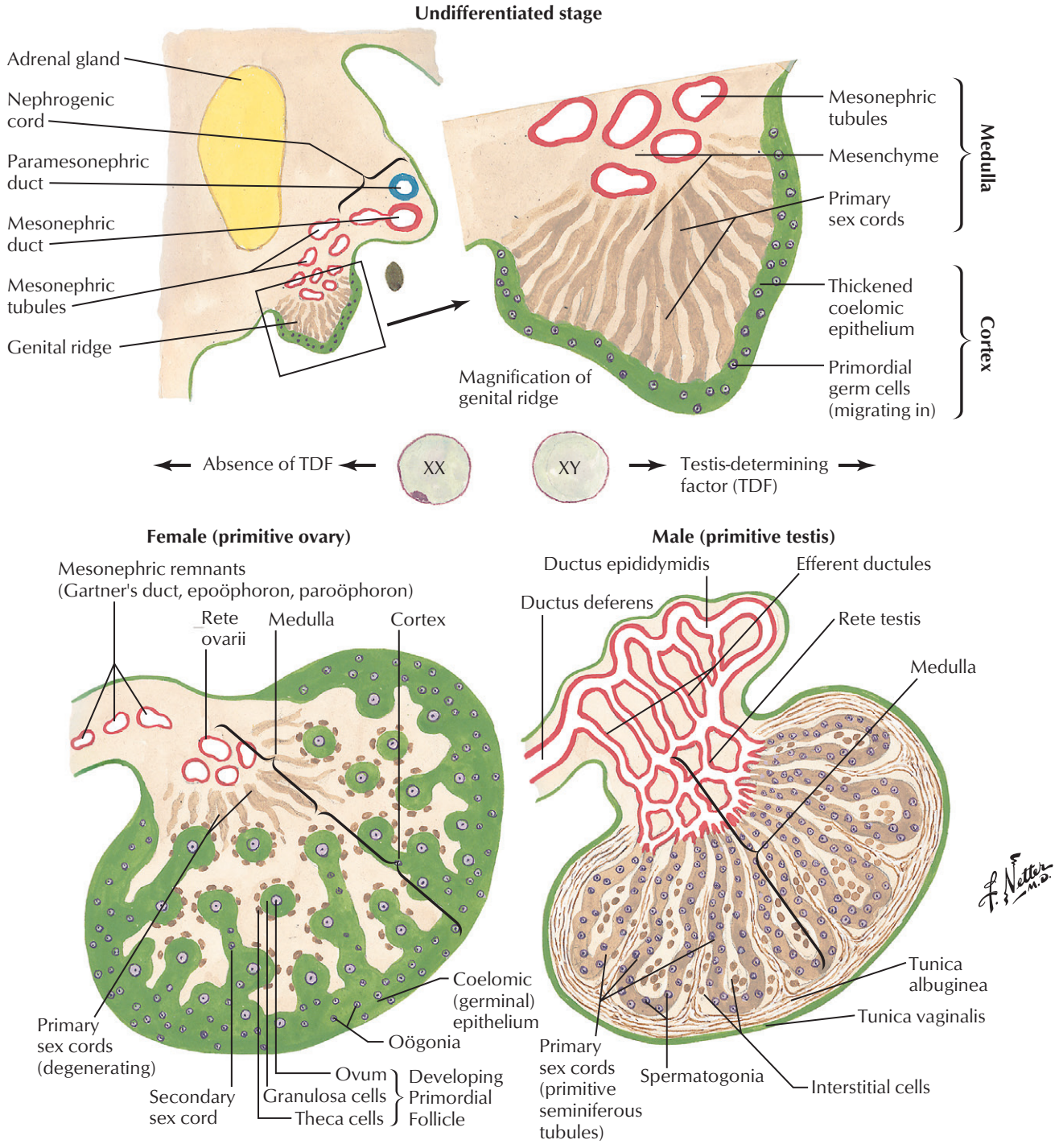


FIGURE 7.20 GONADAL DIFFERENTIATION

The gonads develop from the **gonadal ridge** mesoderm derived from the intermediate mesoderm of the gastrula. The epithelium on the ridge is continuous with the parietal peritoneum (mesothelium). It thickens and projects into the developing gonad in two waves of epithelial sex cords. The **primary sex cords** extend into the medulla and become the **seminiferous tubules** of the testis. They diminish in the female and may persist as a vestigial **rete ovarii. Secondary sex cords** (cortical cords) extend into the ovarian cortex to become **primordial follicles** surrounding the oogonia. Primordial germ cells migrate into the gonads from the gut tube.

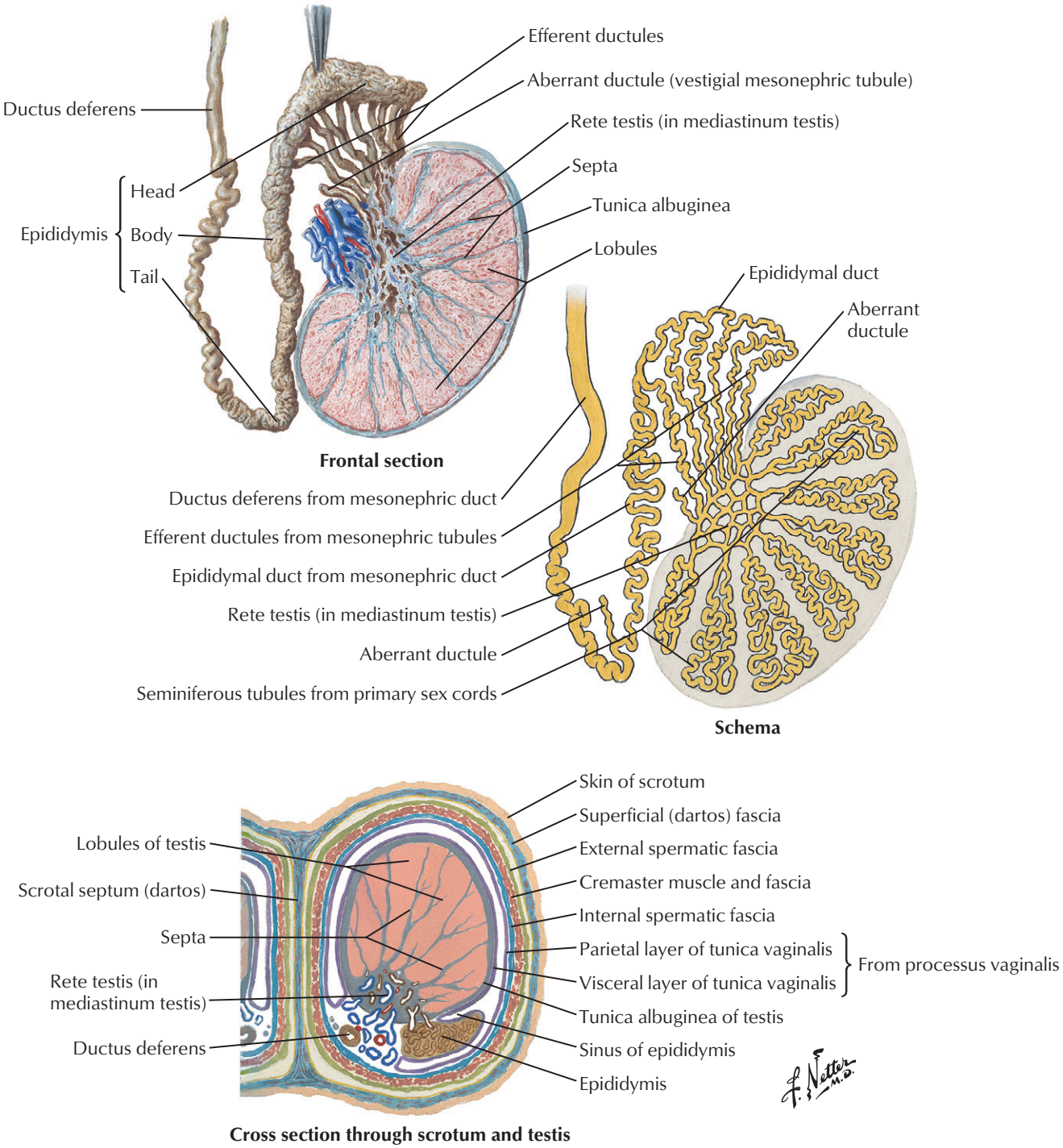


FIGURE 7.21 TESTIS, EPIDIDYMIS, AND DUCTUS DEFERENS

Spermatogonia (primitive male germ cells) are dormant in the seminiferous tubules until puberty, when they increase in number by mitosis and enlarge to become **primary spermatocytes.** Two rounds of meiotic divisions produce two haploid **secondary spermatocytes** and four haploid **spermatids.** The latter are gradually transformed into four mature sperm cells in the process of **spermio-genesis.** The whole process takes approximately 2 months and continues throughout adult life. The gubernaculum guides the descent of the testes through the inguinal canal into the scrotum. They pass behind the peritoneal extension of the **processes vaginalis** that forms the parietal and visceral layers of the tunica vaginalis testis. The visceral layer is closely applied to the tunica albuginea.

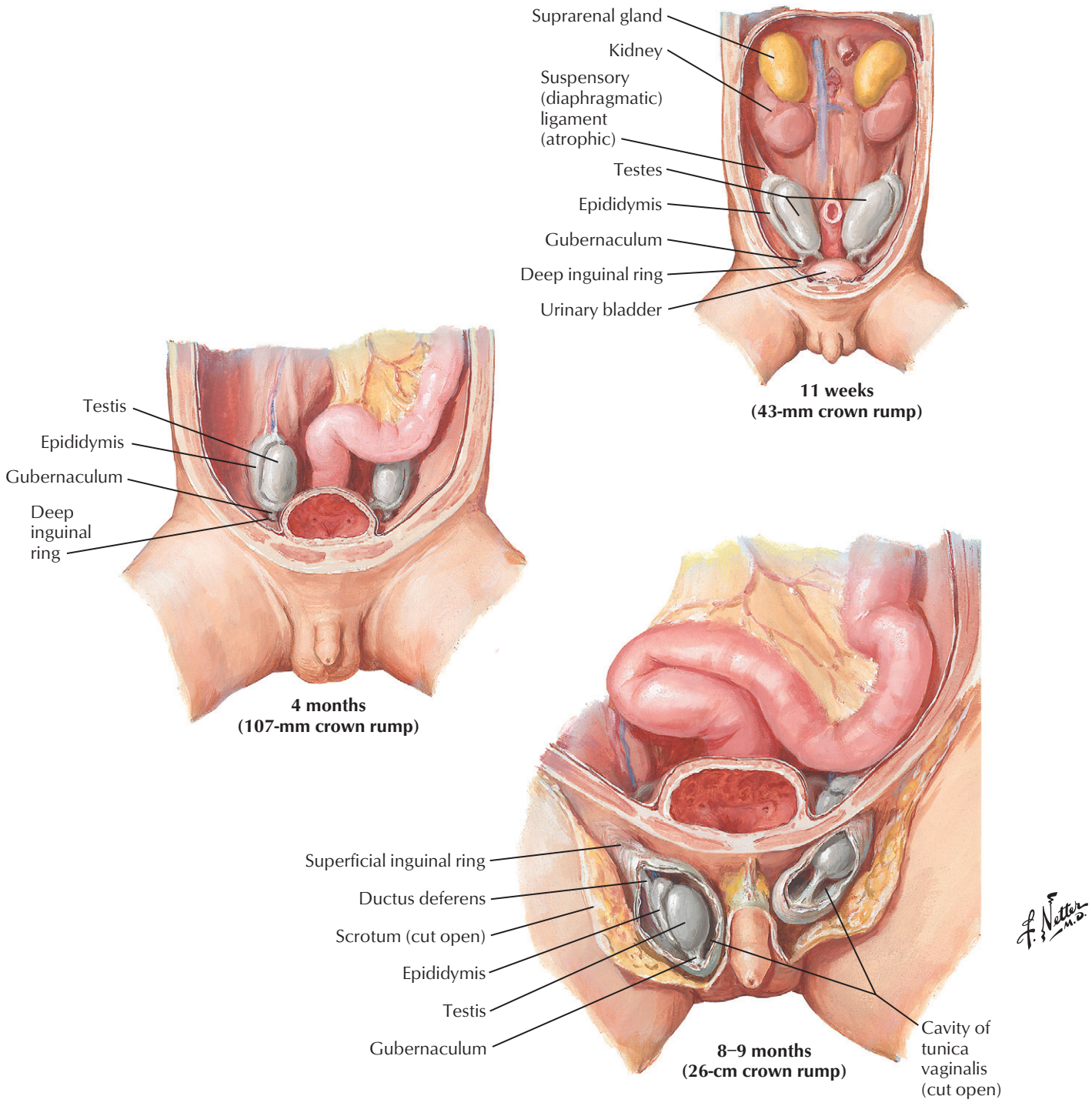


FIGURE 7.22 DESCENT OF TESTIS

The gonads descend in both sexes and are guided by the fibrous **gubernaculum.** The testis passes through the deep body wall into the scrotum via the **inguinal canal** that extends between the deep and superficial inguinal rings (see Chapter 6 for details). It descends behind a fingerlike extension of parietal peritoneum, the **processus vaginalis,** which pinches off around the testis as a coelomic sac in the scrotum called the **tunica vaginalis testis.** The ovary ends up in the mesovarium, an extension of the broad ligament of the uterus in the pelvis. The gubernaculum attaches to the uterus and becomes the fibrous **ovarian ligament** and **round ligament of the uterus.**

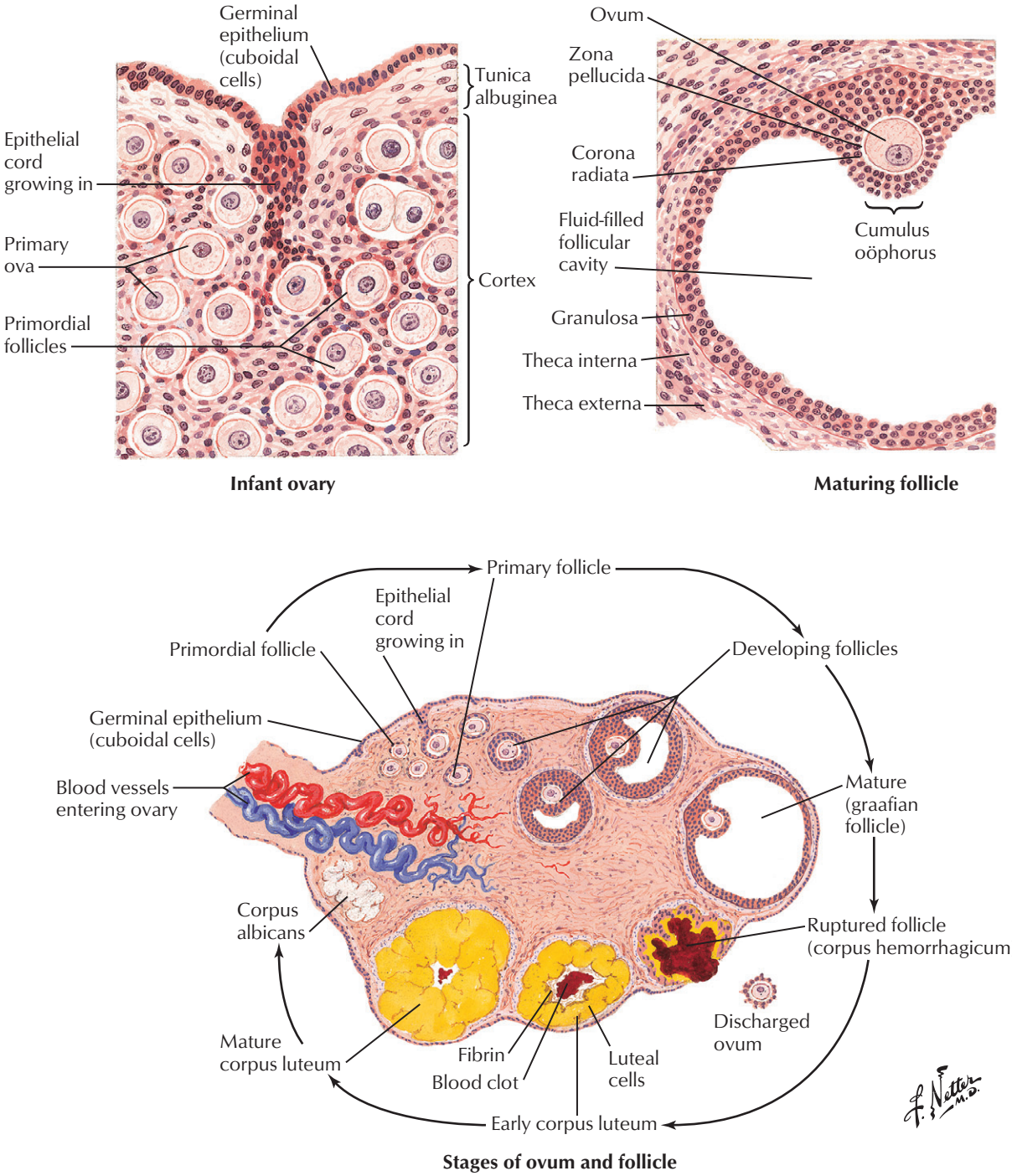
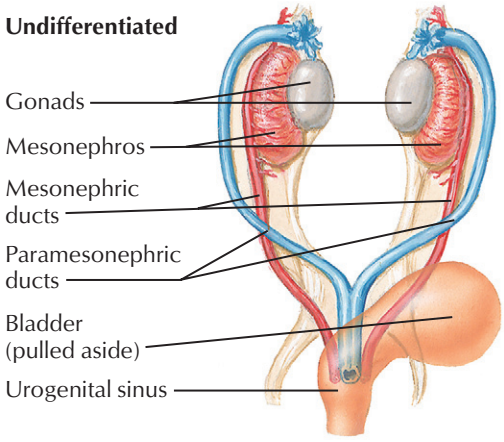
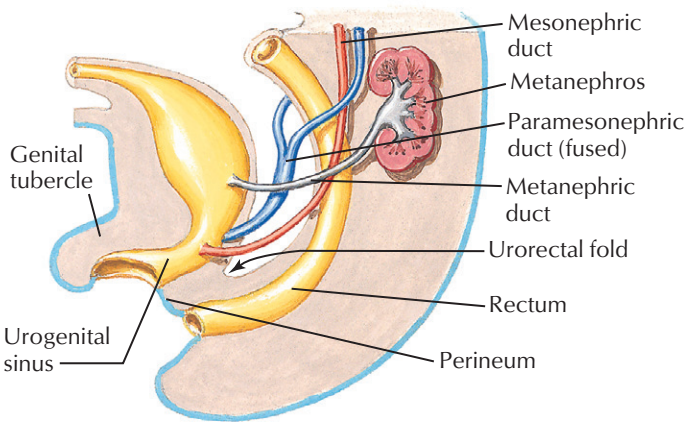


FIGURE 7.23 OVA AND FOLLICLES

Oogonia (primitive oocytes) divide by mitosis in the fetal ovary. Many degenerate, but approximately 700,000 are present at birth and 400,000 at puberty. No new oocytes are produced postnatally. Oogonia become primary oocytes as they complete prophase of the first meiotic division before birth; they remain in that state until after puberty. The first meiotic division is completed just before ovulation and results in a secondary oocyte and small, nonfunctional, polar body. The second meiotic division is arrested in metaphase and is not completed until after fertilization by a sperm. Oocytes develop in follicles that originate from secondary sex cords of epithelium extending from the surface of the ovary. Primordial follicles have a simple squamous epithelium. Mature follicles have a stratified epithelium and may be a centimeter in diameter. The germinal epithelium is continuous with and functionally equivalent to visceral peritoneum.



8-week indifferent stage, anterior view



8-week indifferent stage, lateral view (gonad not shown)

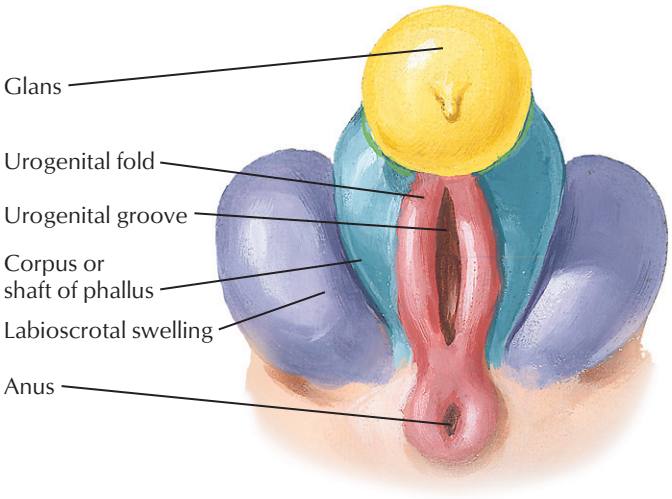
UROGENITAL PRIMORDIA AND DERIVATIVES

Female	Male
From the Urogenital Sinus	
Urinary bladder Urethra Lower vagina (and vaginal epithelium) Vestibule Greater vestibular/urethral glands	Urinary bladder Urethra (except navicular fossa) Prostate gland Bulbourethral glands
	Vestigial: prostatic utricle
From the Mesonephric Duct and Tubules	
Ureteric bud from mesonephric duct forms: Ureter Renal pelvis Major and minor calices Collecting tubules	Efferent ductules Duct of epididymis Ductus deferens Ejaculatory duct Seminal vesicles Ureter, renal pelvis, calices, and collecting tubules
Vestigial: epoophoron, paoophoron, appendix vesiculosa, Gartner's duct	Vestigial: appendix of epididymis
From the Paramesonephric Duct	
Uterine tubes, uterus, upper vagina	Vestigial: appendix of testis
Vestigial: hydatid	

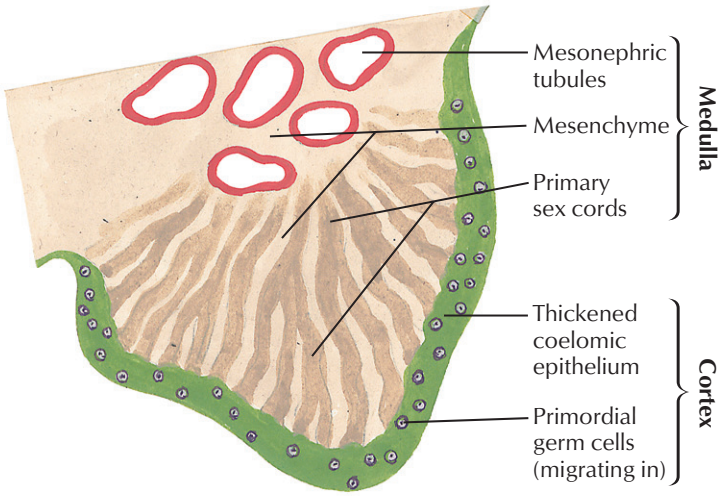
FIGURE 7.24 SUMMARY OF UROGENITAL PRIMORDIA AND DERIVATIVES

A summary of the major concepts of urogenital system development: (1) Gonads and kidneys develop from intermediate mesoderm of the gastrula (genital and nephrogenic ridges). (2) Kidneys form in three successive waves from cranial to caudal. The huge mesonephros is the first functioning kidney. The caudal metanephros is the permanent kidney. (3) Urinary structures develop from the cloaca, a dilation of hindgut splanchnopleure. (4) Both males and females have identical primordia in the 8-week embryo. (5) The mesonephric ducts develop into male internal genital structures; the paramesonephric ducts develop into female internal genital organs. (6) The mesonephric duct changes its function in the male from urinary (mesonephric kidney ureter) to genital (ductus deferens).

10-week external genitalia primordia



Indifferent gonad developing from genital ridge



GENITAL PRIMORDIA AND DERIVATIVES

Female	Male
From the Genital Tubercle/Phallus	
Clitoris: Glans clitoridis Corpora cavernosa clitoridis Bulb of the vestibule	Penis: Glans penis (and navicular fossa) Corpora cavernosum penis Corpus spongiosum penis
From the Urogenital Folds	
Labia minora Perineal raphé Perianal tissue (and external anal sphincter)	Ventral aspect of penis Most of the penile urethra Perineal raphé Perianal tissue (and external sphincter)
From the Labioscrotal Folds	
Labia majora	Scrotum
From the Indifferent Gonad	
Ovary: follicles from secondary sex cords in cortex	Testis: seminiferous tubules from primary sex cords Rete testis in medulla
Vestigial: rete ovarii in medulla	
From the Gubernaculum	
Ovarian ligament Round ligament of the uterus	Gubernaculum testis

F. Netter M.D.

FIGURE 7.25 SUMMARY OF GENITAL PRIMORDIA AND DERIVATIVES

A summary of major concepts of genital development: (1) The external genital organs develop from three swellings of somatopleure: a genital tubercle, urogenital (UG) folds, and labioscrotal folds. (2) The urethra in the male comes from two primordia: the UG sinus that closes on the ventral surface of the penis and an invagination of ectoderm at the end of the glans. (3) The urethra, vestibule, and lower vagina come from the UG sinus in females. (4) There are two waves of epithelial sex cords in the primitive gonad. The primary wave forms the seminiferous tubules of the testis. A secondary wave forms follicles surrounding oocytes in the ovary. The epithelium of the original genital ridge persists as the "germinal" epithelium of the ovary.

Terminology

Allantois	(G., "sausage-like") A vestigial, endodermal extension of the cloaca into the umbilical cord in mammals. In egg-laying animals, it lines the inner surface of the egg for gas exchange.
Appendix of the testis	A remnant of the paramesonephric duct in the male. It is attached to the superior pole of the testis.
Appendix vesiculosa	Persistence of the cranial end of the mesonephric (wolffian) duct in females lateral to the ovary/epoöphoron.
Bicornuate	(L, "two horns") Double uterus characteristic of most mammals, but an anomaly in primates whose single uterus comes from fused paramesonephric (müllerian) ducts.
Bowman's capsule	The epithelial covering of the glomerular capillaries. It has a visceral layer of podocytes and simple squamous parietal layer. The urinary space between the two continues into the proximal convoluted tubule of the nephron.
Cloaca	(L., "sewer") A dilation at the caudal end of the hindgut that divides to form the rectum, urinary bladder, urethra, vestibule, prostate, and related structures.
Cryptorchidism	(G., "hidden testis") An undescended testis not in the scrotum.
Epoöphoron	Remnants of mesonephric tubules and a segment of mesonephric duct between the ovary and uterine tube. These correspond to efferent ductules and duct of the epididymis in males.
Gartner's duct	Remnants of the mesonephric duct in the broad ligament of the uterus. They may form cysts.
Germinal epithelium	A term for the epithelium on the surface of the ovary. It was thought that this epithelium gave rise to primordial germ cells (oogonia). Follicular cells come from ovarian epithelium, but the germ cells migrate from the wall of the gut tube into the ovary.
Glomerulus	Tuft of capillaries in the in the renal corpuscle of a nephron where urine is filtered from the blood.
Hydatid (of Morgagni)	A persistent part of the cranial end of the paramesonephric (müllerian) duct that does not contribute to the uterine tube.
Hymen	A membrane that is a remnant from a secondary cavitation of the vagina after endodermal cells from the urogenital sinus fill the lumen of lower part of the uterovaginal primordium (from the fused paramesonephric ducts). It is not a vestige of the cloacal membrane.
Hypospadias	Failure of the urogenital folds to fuse completely on the ventral surface of the penis in the formation of the penile urethra. Urine escapes from a ventral opening in the newborn penis.
Indifferent stage	The 8-week embryo that has identical primordial in both sexes. As embryos of each sex develop, they lose the primordial of the opposite sex.
Intermediate mesoderm	Mesoderm in the gastrula between the paraxial column and lateral plate that gives rise to the kidneys and gonads.

Terminology, cont'd

Mesonephros	(G., "middle kidney") The first functioning kidney in the embryo, it develops from the intermediate mesoderm of the gastrula and is closely applied to the primitive gonad. It disappears as the permanent metanephric kidney forms. In the male, the mesonephric duct and tubules become connected to the testis to form the male genital duct system (e.g., ductus deferens, ejaculatory duct).
Nephron	The structural and functional unit of the kidney where urine is filtered from the blood, concentrated, processed, and transported. In sequence, it consists of a glomerulus, proximal convoluted tubule, Henle's loop, and a distal convoluted tubule that connects with a collecting tubule.
Paramesonephric (müllerian) duct	Primordium of the uterine tubes, uterus, and upper vagina.
Paroöphoron	Remnants of mesonephric tubules medial to the ovary and the location of the vestigial epoöphoron.
Pronephros	(G., "first kidney") The first kidney to develop at the cranial end of the intermediate mesoderm. It has a brief existence and never functions.
Prostatic utricle	A midline, blind pouch off the prostatic urethra that is the remnant of the caudal end of the paramesonephric duct. The male equivalent of the vagina.
Renal corpuscle	Glomerular capillaries surrounded by Bowman's capsule, the site of filtration of urine from the bloodstream in the cortex of the kidney.
Sinovaginal bulbs	Paired outgrowths of the sinus tubercle of the urogenital sinus at the base of the uterovaginal primordium that are induced by contact of the fused paramesonephric ducts with the urogenital sinus. They form a solid endodermal vaginal plate at the bottom of the vagina that cavitates and gives rise to all of the vaginal epithelium.
Sinus tubercle	Swelling of the ruogenital sinus in which the left and right paramesonephric ducts contact the sinus.
Urachus	Fibrous remnant of the allantois extending from the top of the bladder to the umbilicus.
Urogenital sinus	The anterior product of the division of the cloaca that consists of the primitive urinary bladder, a pelvic portion, and a lower genital portion (urogenital sinus proper) that gives rise to the urethra and all related glands in both sexes and the vestibule and lower vagina in the female.
Urogenital folds	Primordia that give rise to the labia minora surrounding the vestibule in the female and the penile urethra and ventral penis in the male.
Urorectal septum	The tissue in the natural cleft between the allantois and hindgut tube. It extends inferiorly to divide the cloaca into the rectum and a urogenital sinus that becomes urinary bladder, urethra, vestibule, prostate, and related structures.

CHAPTER 8

THE MUSCULOSKELETAL SYSTEM

Primordia for the Skeletal System

Sclerotome of somites, somatopleure mesoderm, and neural crest cells in the head (forming pharyngeal arch mesenchyme and general head mesenchyme).

Primordia for Skeletal Muscles

Myotome of somites and somitomeres; somatopleure mesoderm and neural crest–derived head and pharyngeal arch mesenchyme.

Primordia for Heart and Smooth Muscle

Cardiogenic mesoderm from the primitive streak for the heart and most all sources of mesoderm for smooth muscle.

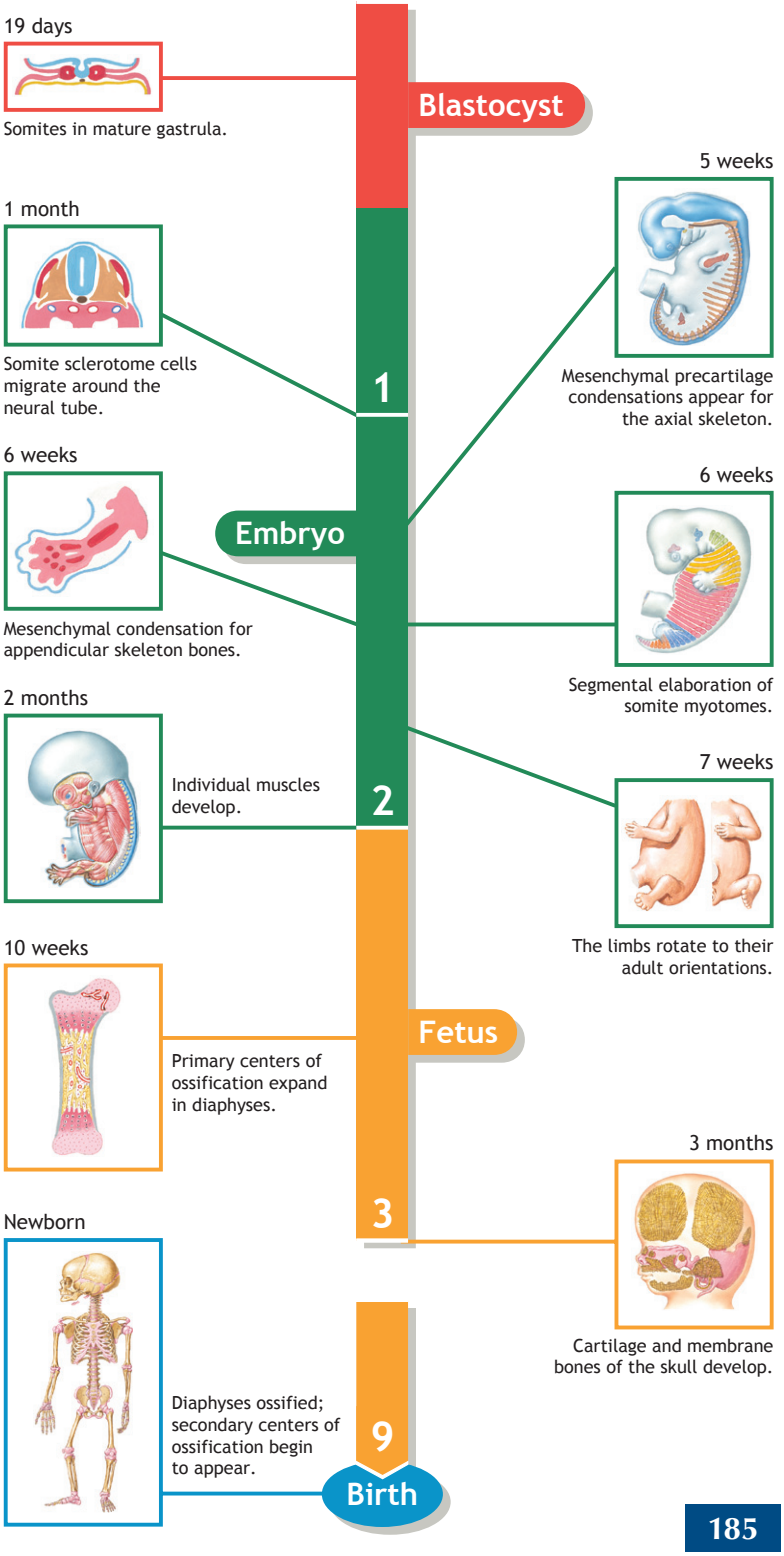
Plan

Most bones of the postcranial skeleton form as cartilaginous models that are replaced by bone tissue. Most bones of the skull form in mesenchyme membranes because cartilage is not suitable to accommodate the dynamic forces of the growing brain and face.

The pattern of the developing muscular system is intimately involved with the plan of the peripheral nerves. The two primary themes are the segmental nature of muscle formation from somite myotomes and the division of myotomes to form muscle groups, each with its own branch of a spinal nerve. Each myotome divides to form an epimere (with its dorsal nerve ramus) and a hypomere (with its ventral ramus). The epimere forms the intrinsic back muscles, whereas the hypomere forms the lateral and ventral trunk muscles, including all limb muscles. The hypomere in the limbs further divides to form the flexor and extensor compartment muscles of the limbs (with their anterior and posterior division nerves, respectively).

TIMELINE

Prenatal Time Scale (Months)



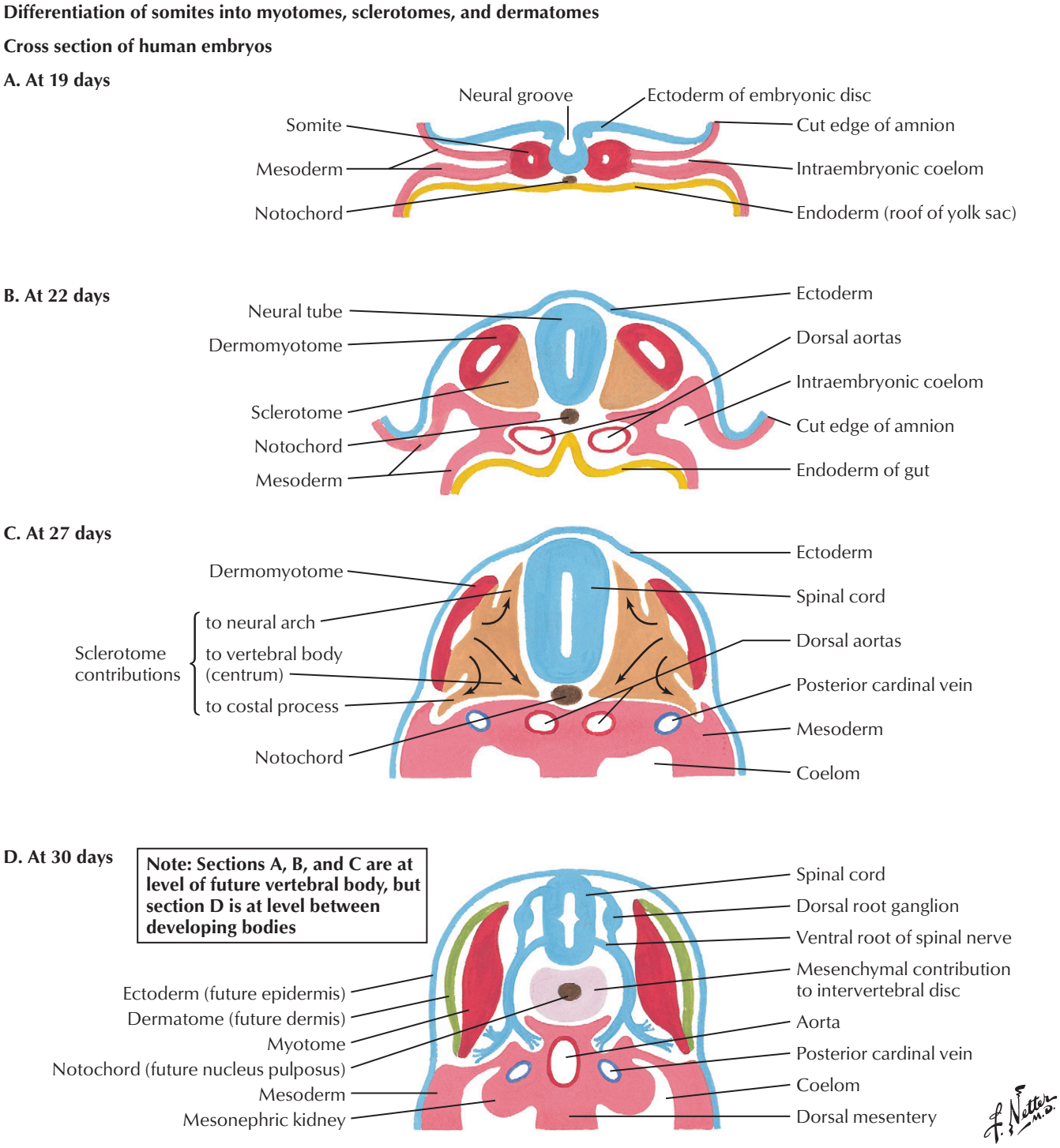


FIGURE 8.1 MYOTOMES, DERMATOMES, AND SCLEROTOMES

Bone, muscle, and connective tissue primarily come from primitive streak mesoderm, including somites, lateral plate mesoderm, and diffuse mesenchyme produced during gastrulation. Cells on the deep aspect of the somites begin to dissociate and migrate around the neural tube and notochord and into the somatopleure. These sclerotome cells differentiate into chondroblasts that form the cartilaginous precursors of the axial skeleton and bones of the cranial base. The remnant of each somite is a dermomyotome that separates into a dermatome and a muscle-forming myotome. The dermatome becomes the connective tissue dermis of the skin.

Progressive stages in formation of vertebral column, dermatomes, and myotomes

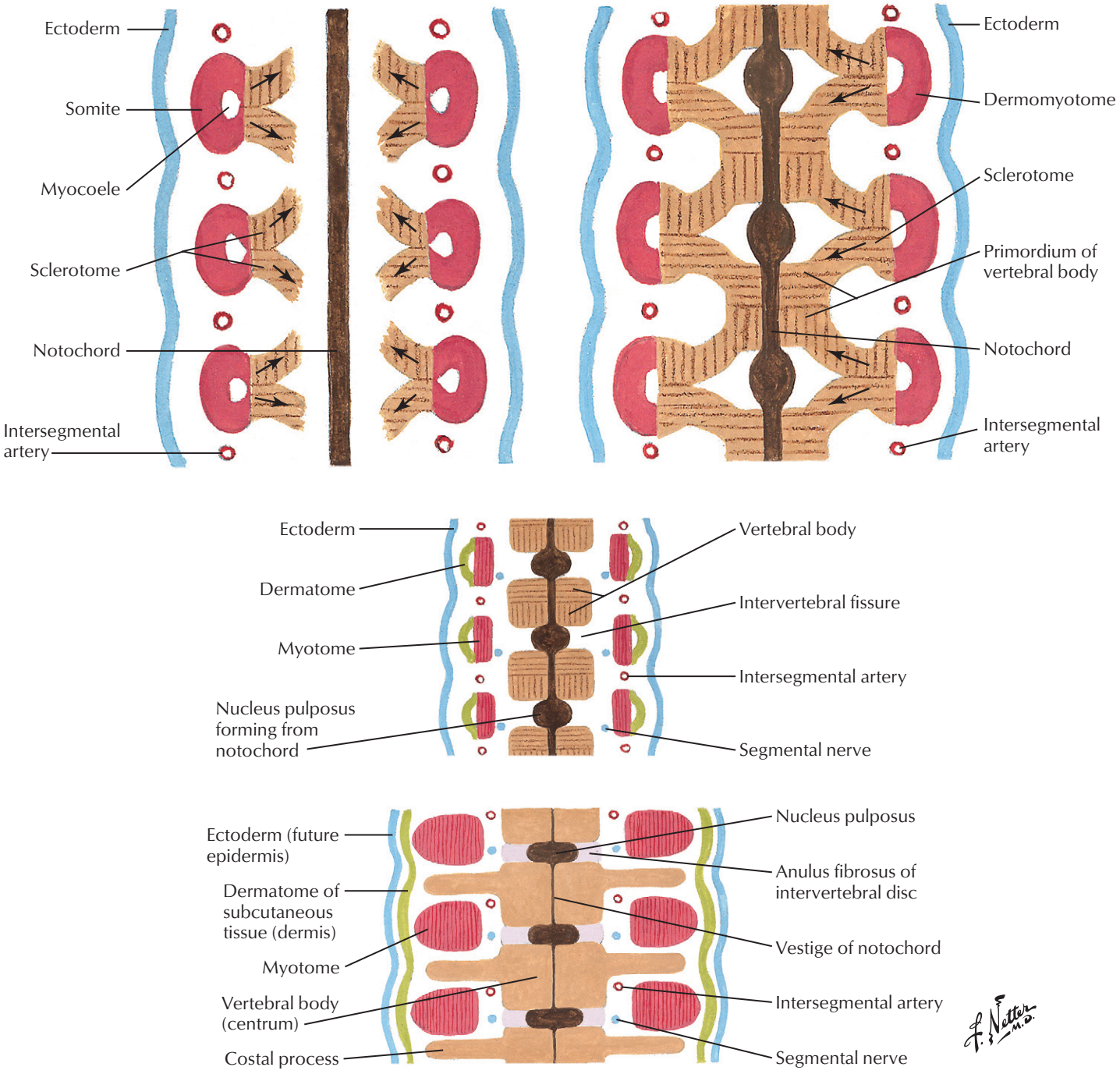
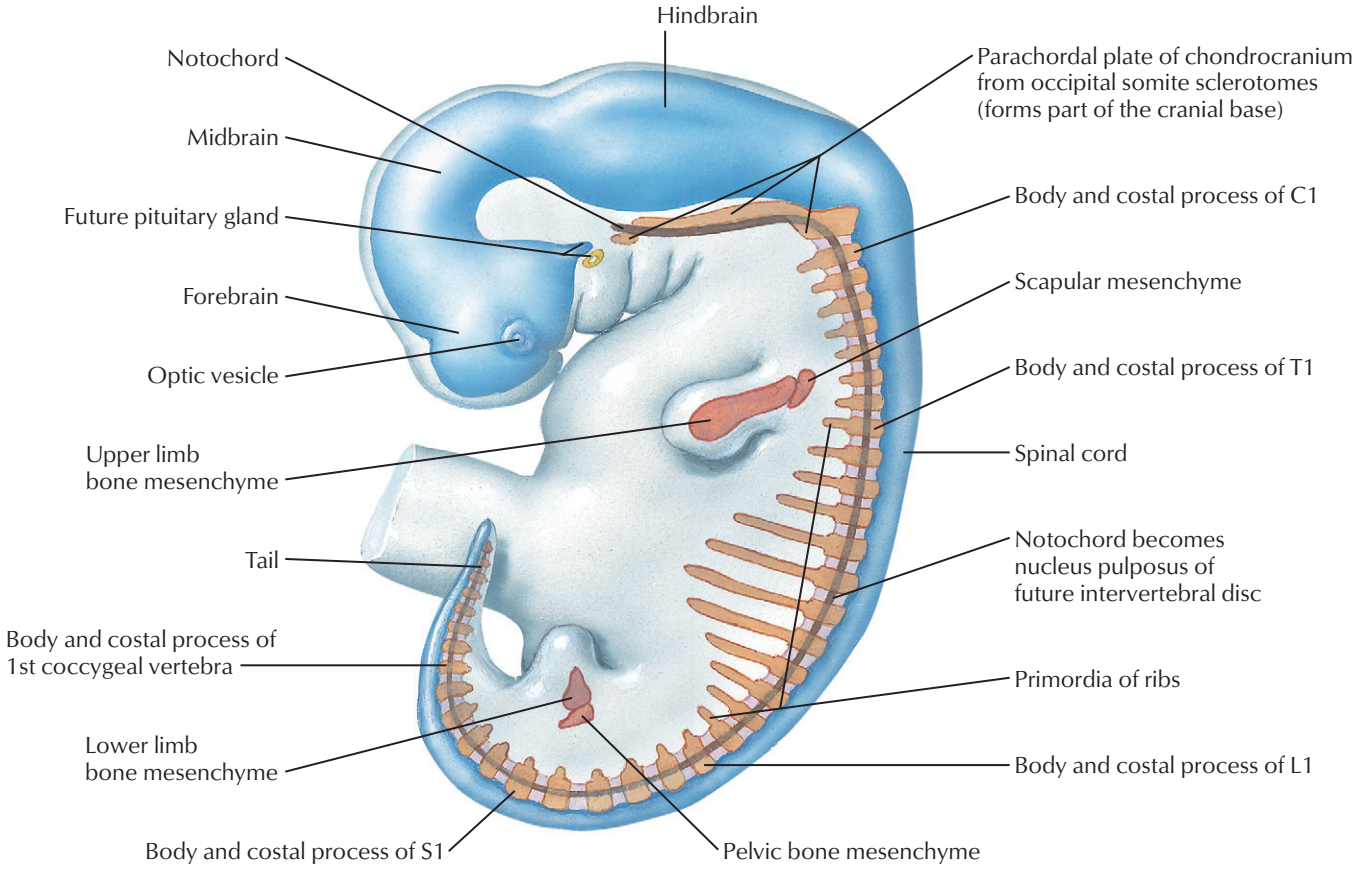


FIGURE 8.2 MUSCLE AND VERTEBRAL COLUMN SEGMENTATION

The dermatomes form connective tissue below the surface ectoderm, the primordium of the epidermis of the skin. The myotomes differentiate into segmental muscle masses, and the sclerotome and notochord form the vertebral column. The body (centrum) of a vertebra comes not from a single sclerotome, but from the fusion of two halves of adjacent sclerotomes. This is the most notable morphological example of segmental gene products expressed as *parasegments* that overlap adjacent early segments. The result is that the intervals between the vertebral bodies are at the level of the myotomes, and the spinal nerves that exit the vertebral column have a direct path to their muscle targets.

Mesenchymal precartilage primordia of axial and appendicular skeletons at 5 weeks



Precartilage mesenchymal cell condensations of appendicular skeleton at 6th week

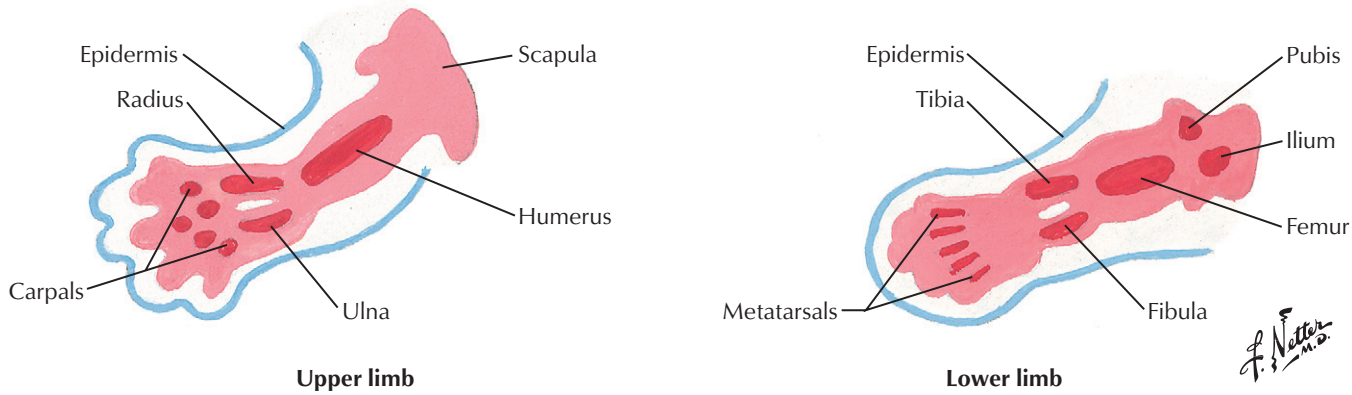


FIGURE 8.3 MESENCHYMAL PRIMORDIA AT 5 AND 6 WEEKS

Bone development begins with condensations of mesenchyme from sclerotomes (for the axial skeleton) and somatopleure (for the appendicular skeleton). Cells from these condensations differentiate into chrondroblasts that convert the mesenchymal primordia into cartilaginous precursors of the bones. The cartilage eventually is replaced by bone through **endochondral ossification.** The sclerotomes extend into the embryonic head to form endochondral bone at the base of the neurocranium. Most other bones of the skull form by **intramembranous (mesenchymal) ossification,** the direct deposition of bone in mesenchyme derived from the neural crest.

Fate of body, costal process, and neural arch components of vertebral column, with sites and time of appearance of ossification centers

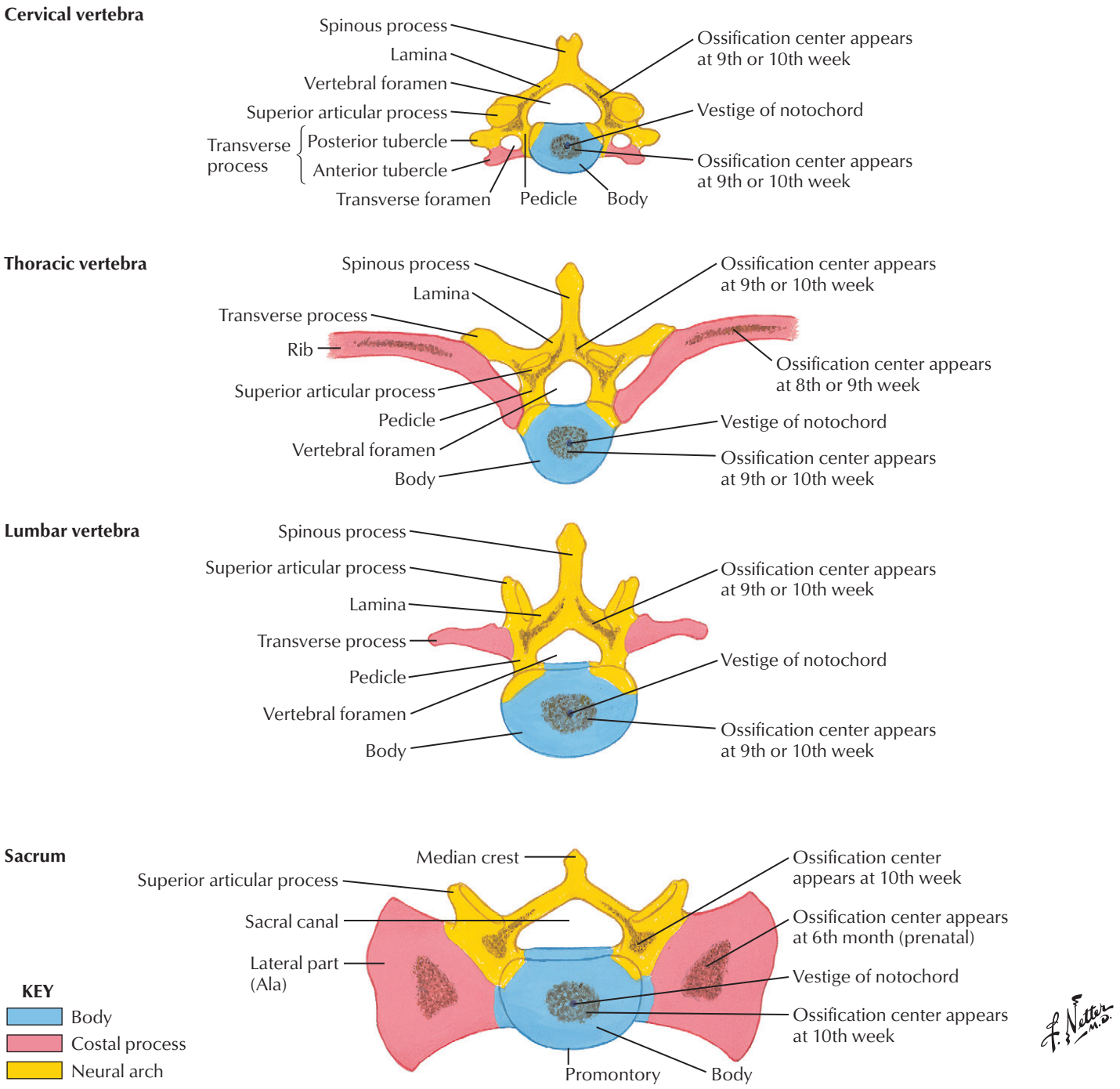


FIGURE 8.4 OSSIFICATION OF THE VERTEBRAL COLUMN

Bone first appears in the hyaline cartilage models in local **ossification centers,** where the cartilage is broken down and removed and osteoblasts begin to deposit bone tissue. Most bones develop from a number of ossification centers. The vertebral column develops from ossification centers in the body, the neural arch, and the costal process of cartilage of each vertebra and pair of ribs. In vertebrae without rib articulations, the costal processes contribute to the transverse processes of the vertebrae or the lateral alae (wings) of the sacrum. The notochord mostly disappears; it persists only as the nucleus pulposis, the gelatinous center of an intervertebral disc.

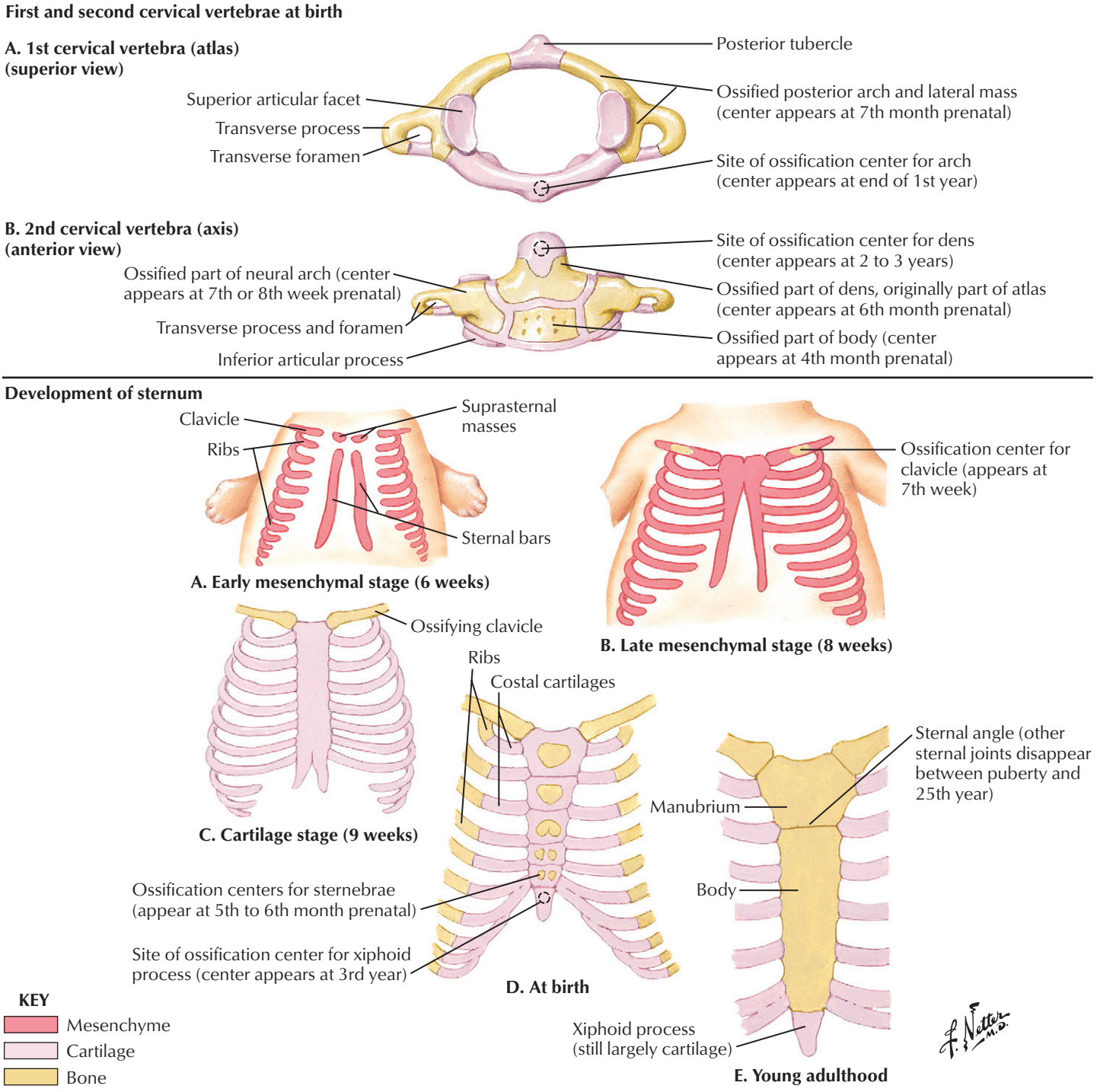


FIGURE 8.5 DEVELOPMENT OF THE ATLAS, AXIS, RIBS, AND STERNUM

The atlas (C1) and axis (C2) differ from typical vertebrae in that the body (centrum) of the atlas fuses to the body of the axis as the odontoid process (dens), the "axis" around which the atlas and skull rotate. The clavicle is the only postcranial bone that develops in mesenchyme instead of cartilage. Sternum development is unusual in that it progresses from paired mesenchymal condensations, a single piece of cartilage, and a vertical series of ossification centers that are also paired. Rib ossification is also unique. Hyaline cartilage remains between rib bodies and the sternum as the costal cartilages, but the sternocostal joints are synovial.

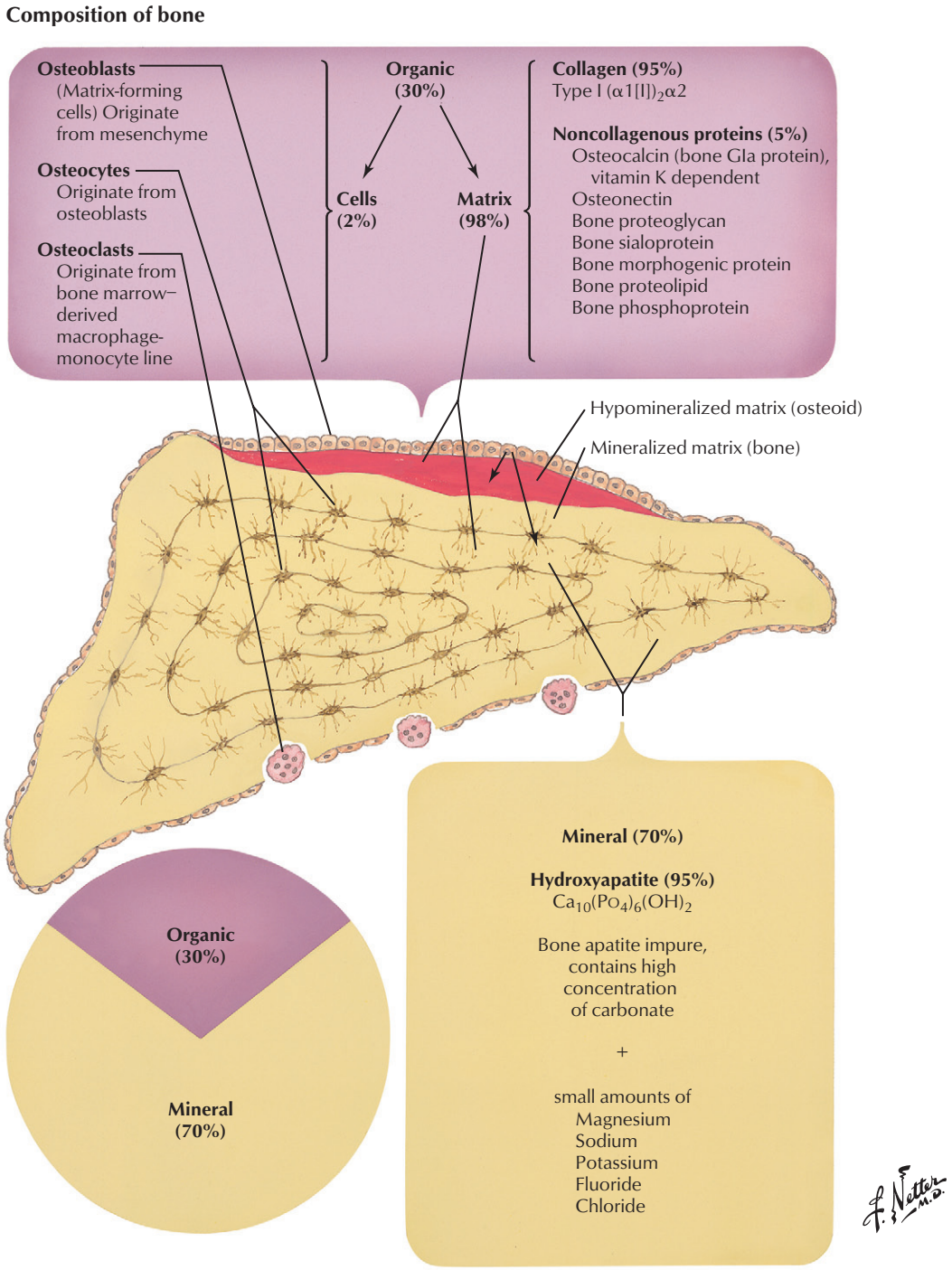


FIGURE 8.6 BONE CELLS AND BONE DEPOSITION

The development of bone and the remodeling of adult bone involve the cellular processes of bone deposition and resorption. **Osteoblasts** deposit bone on surfaces, **osteocytes** maintain bone in spaces called lacunae within the bone matrix, and multinucleated **osteoclasts** resorb bone on surfaces. The organic component of bone, called **osteoid,** is deposited first and later mineralized by membrane-bound packets of **hydroxyapatite crystals** left in the osteoid by the osteoblasts.

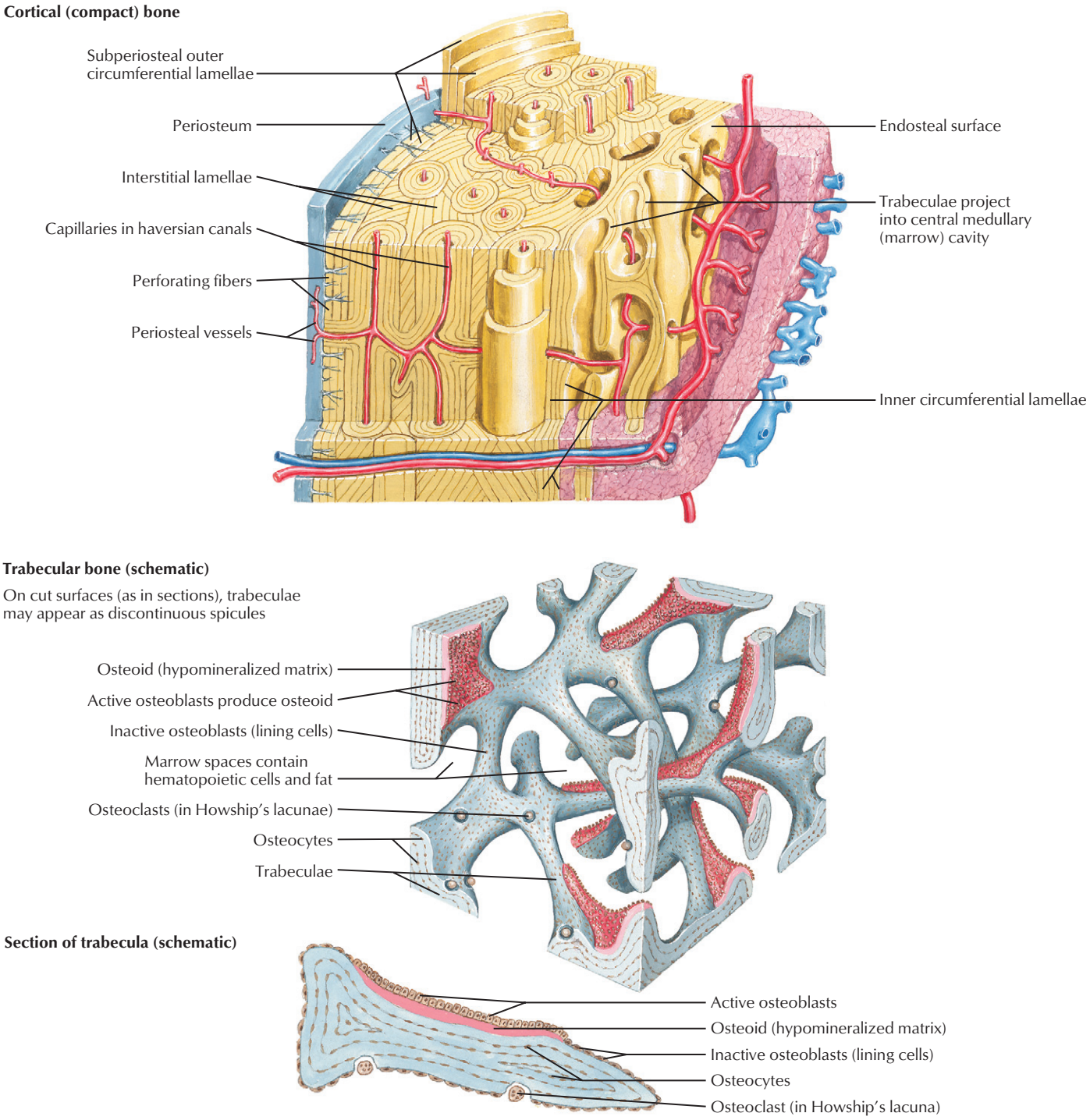


FIGURE 8.7 HISTOLOGY OF BONE

Endochondral and intramembranous ossification produce the same bone tissues. Most adult bones have **compact bone** on the outside and **spongy** (**trabecular** or **cancellous**) **bone** on the inside. Adult compact bone consists of layers of bone called **lamellae** that are separated from each other by thin layers of aligned collagen fibers. **Circumferential lamellae** envelop the compact layer and long, cylindrical, concentric lamellae form **osteons (Haversian systems),** the structural units of compact bone. Between osteons are **interstitial lamellae** that are the remaining segments of older osteons. Surrounding the bone is **periosteum** consisting of an outer fibrous layer and inner osteogenic layer with osteoblasts. **Endosteum** lines the inner, more irregular surface of compact bone.

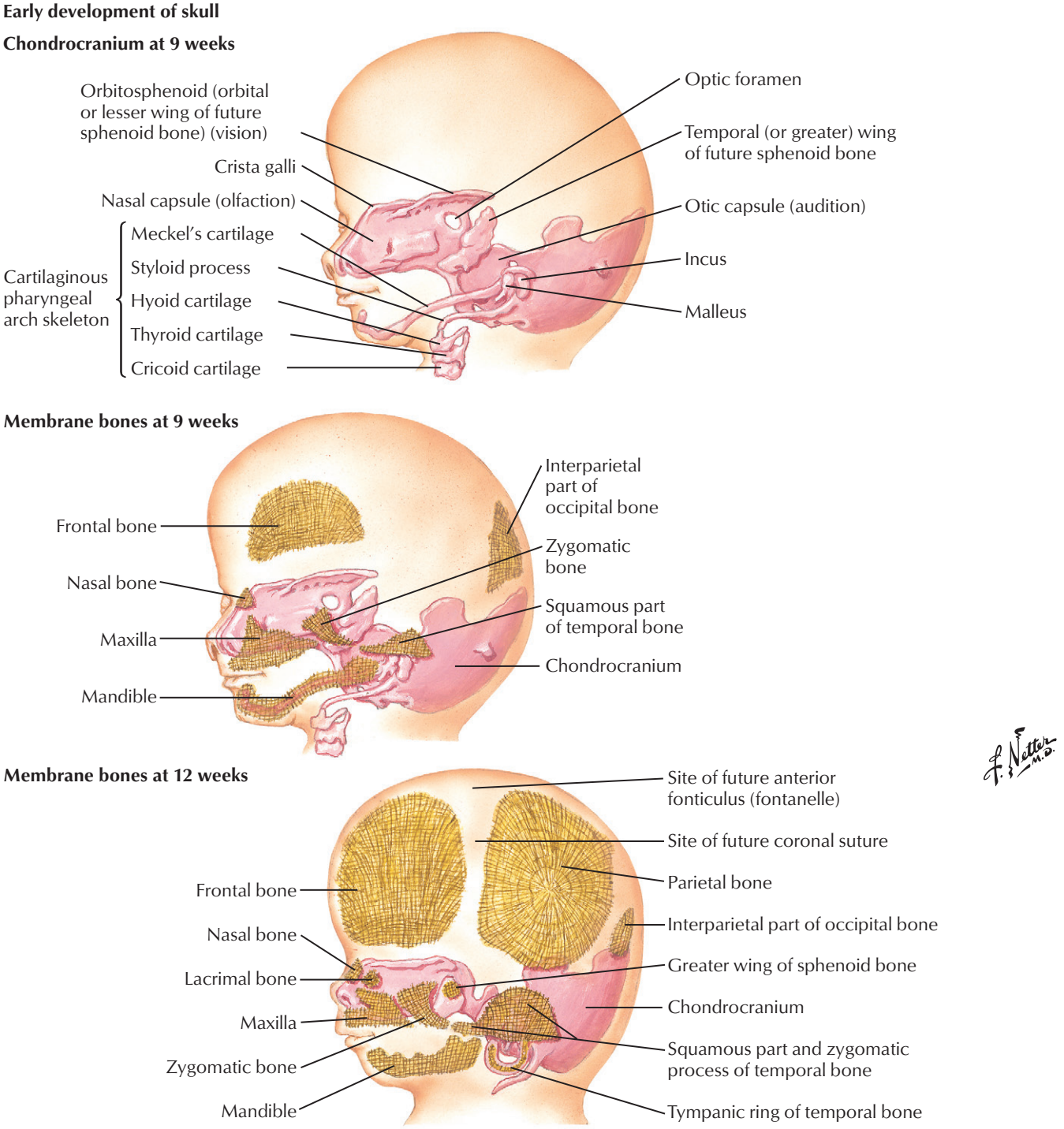


FIGURE 8.8 MEMBRANE BONE AND SKULL DEVELOPMENT

Most postcranial bones and the bones of the cranial base develop via endochondral ossification, whereas most bones of the neurocranium and viscerocranium develop directly from mesenchyme. **Mesenchymal bone formation** is often called **intramembranous ossification,** a misleading term derived from the connective tissue membrane surrounding the developing brain in which ossification centers develop for the flat neurocranial bones. The bones of the facial skeleton and part of the clavicles develop in mesenchyme that does not have a membranous appearance, and the term *membrane* does not characterize the microscopic environment of mesenchymal bone development.

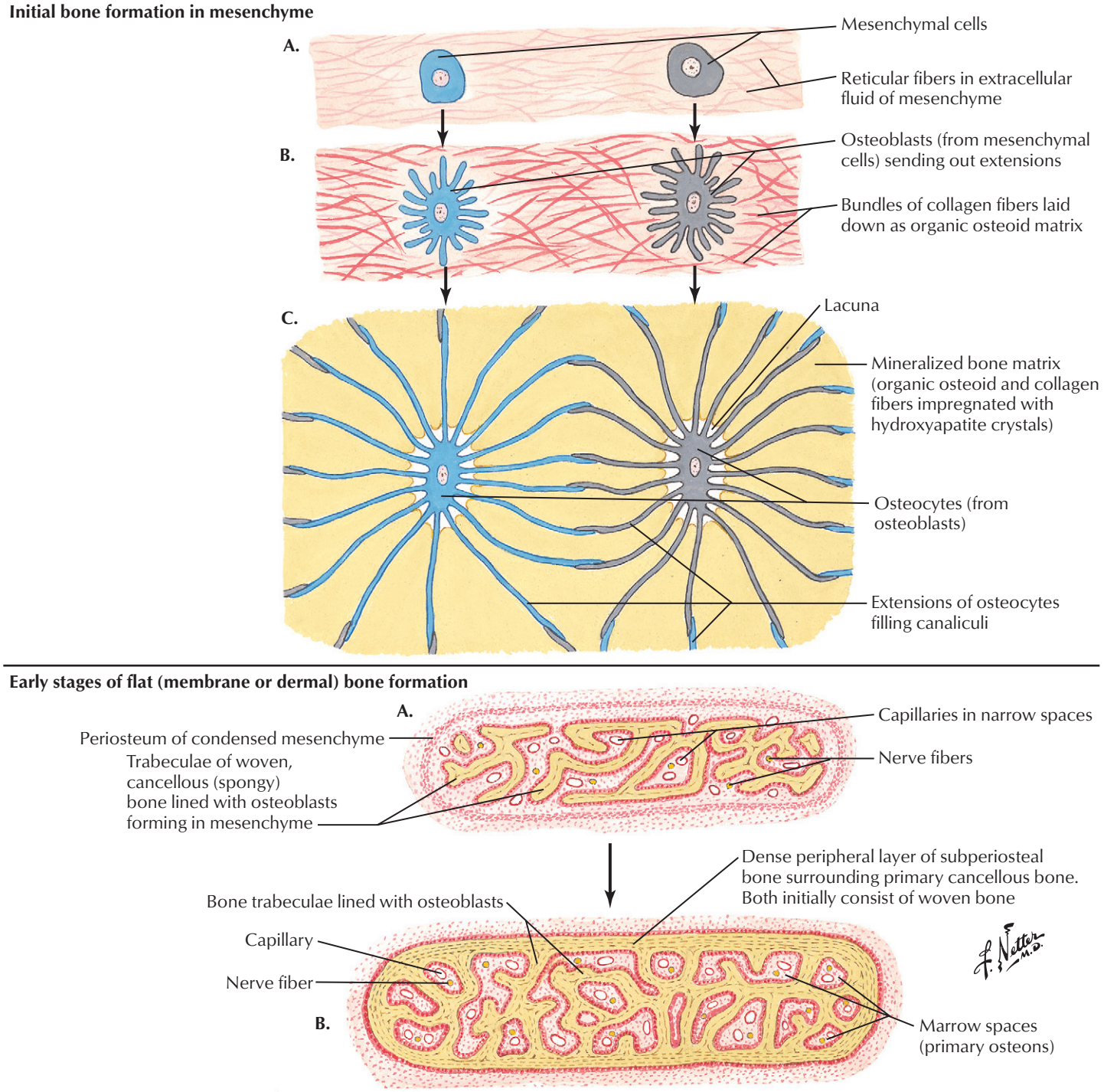


FIGURE 8.9 BONE DEVELOPMENT IN MESENCHYME

Mesenchymal cells in the embryonic head differentiate into osteoblasts that develop processes and deposit **osteoid,** the organic matrix of bone. Inorganic hydroxyapatite crystals are incorporated into the osteoid to form mineralized, true bone tissue. The osteoblasts become osteocytes in spaces called **lacunae,** and their processes are metabolically coupled with those of other cells in **canaliculi.** Trabecular bone with thin spicules surrounded by vascular marrow is the first bone to form. This bone is also called **woven bone** because it lacks lamellae—the collagen fibers have a random, "woven" arrangement. All bone is woven bone when first deposited.

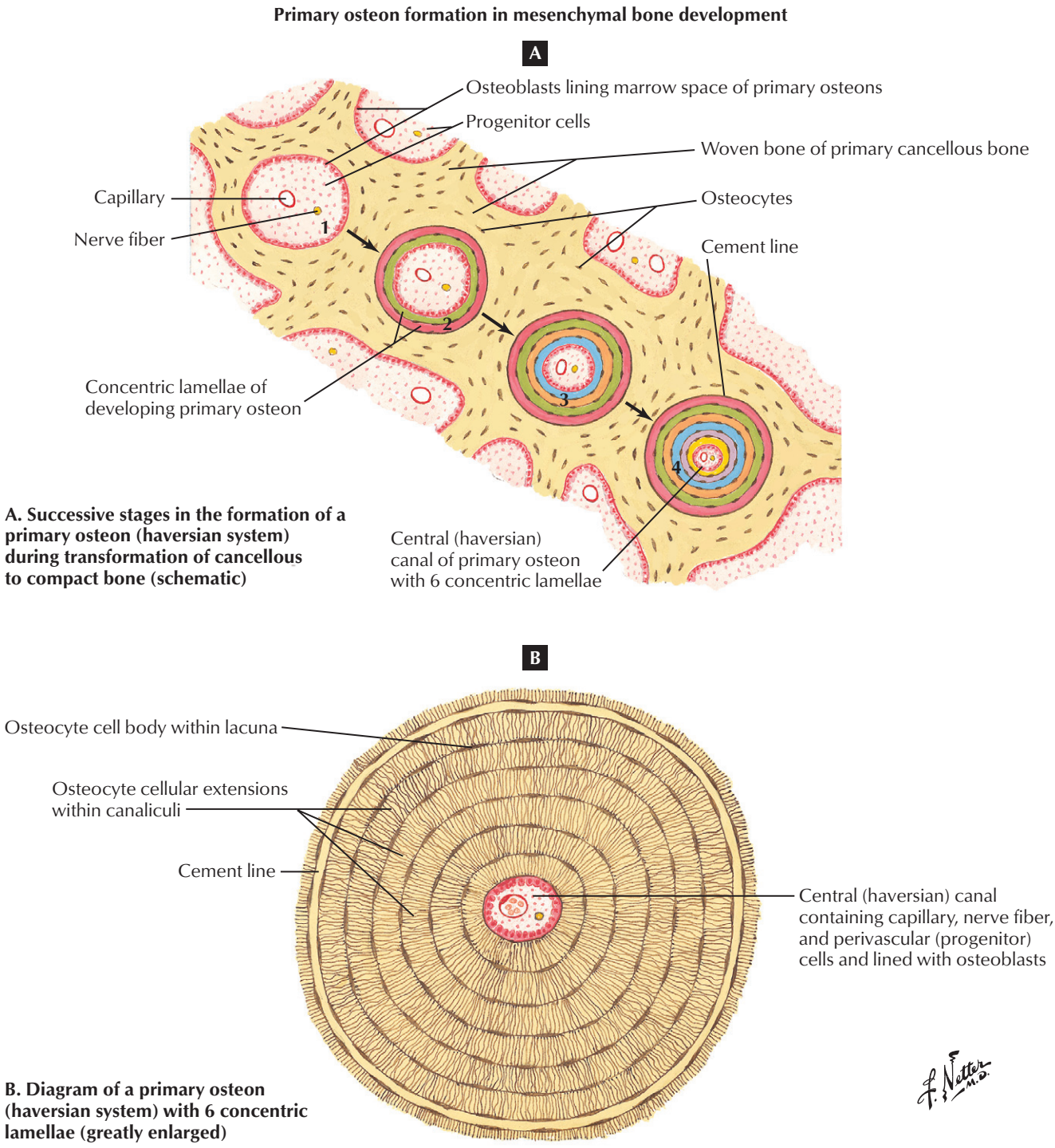


FIGURE 8.10 OSTEON FORMATION

Osteons form in developing compact bone as a way to bring a blood supply into thicker compact bone regions via their central **haversian canals** and interconnecting **Volkmann's canals.** Primary osteons are the first osteons to form in tunnel-shaped marrow spaces within the original trabecular bone; these marrow spaces will be filled in with concentric layers of lamellae. Subsequently, secondary osteons are formed by a remodeling process (p. 196). In both primary and secondary osteon formation, the outermost lamellae are deposited first, followed by successive layers toward the central canal.

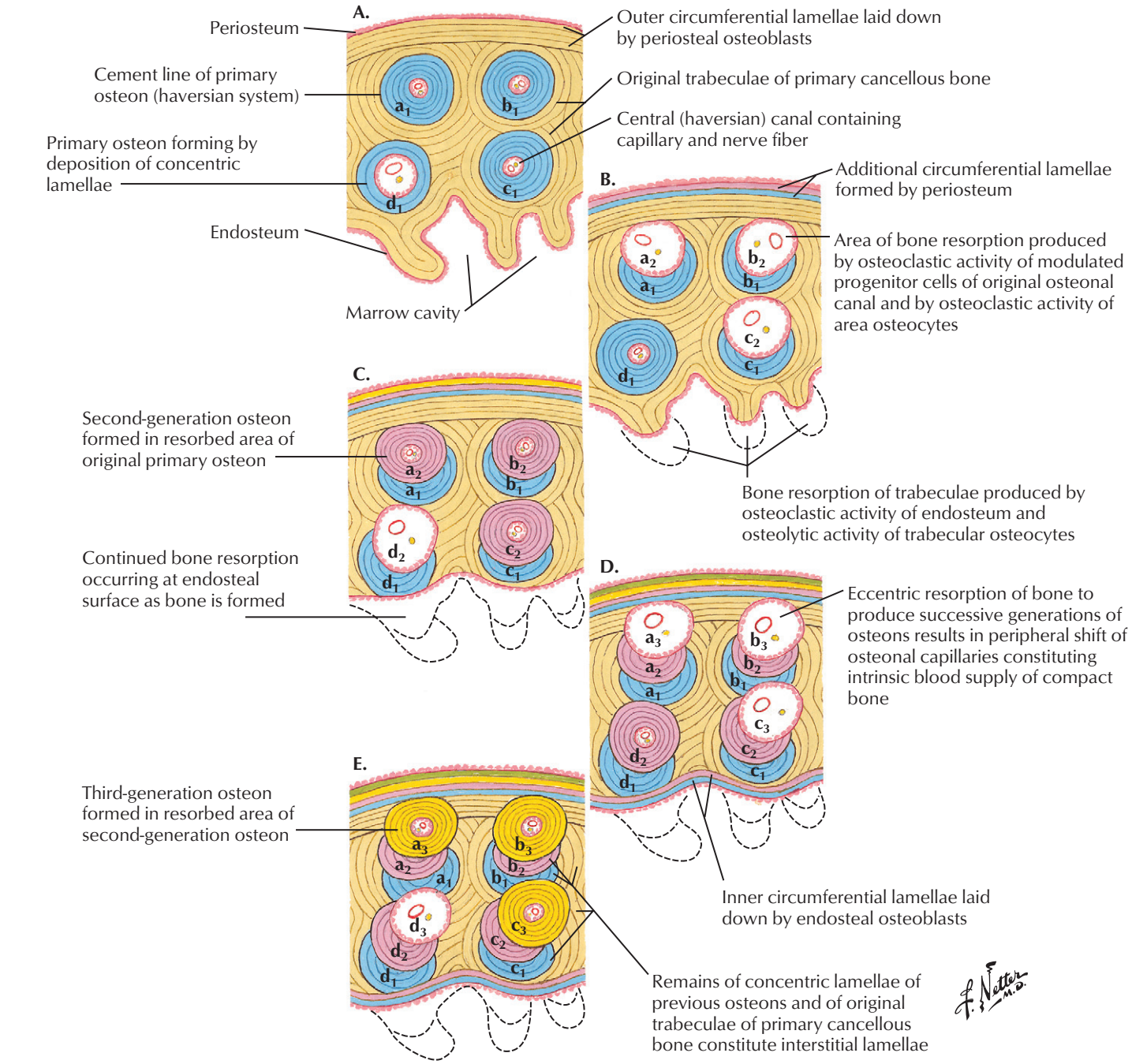


FIGURE 8.11 COMPACT BONE DEVELOPMENT AND REMODELING

Cartilage can expand by **interstitial growth** (i.e., the addition of a new matrix from within). Bone can grow only by deposition of bone on surfaces **(appositional growth).** When a bone grows in width, new circumferential lamellae are deposited on the outer surface of compact bone by the osteogenic layer of periosteum; the trabeculae and the inner surface are resorbed by osteoclasts.

New, **secondary osteons** form near the surface by a remodeling process similar to the natural turnover in osteons that occurs throughout life. New generations of osteons form when osteoclasts excavate a tunnel the diameter of the new haversian system, and lamellae are deposited from the outside to the inside in a manner similar to the formation of primary osteons.

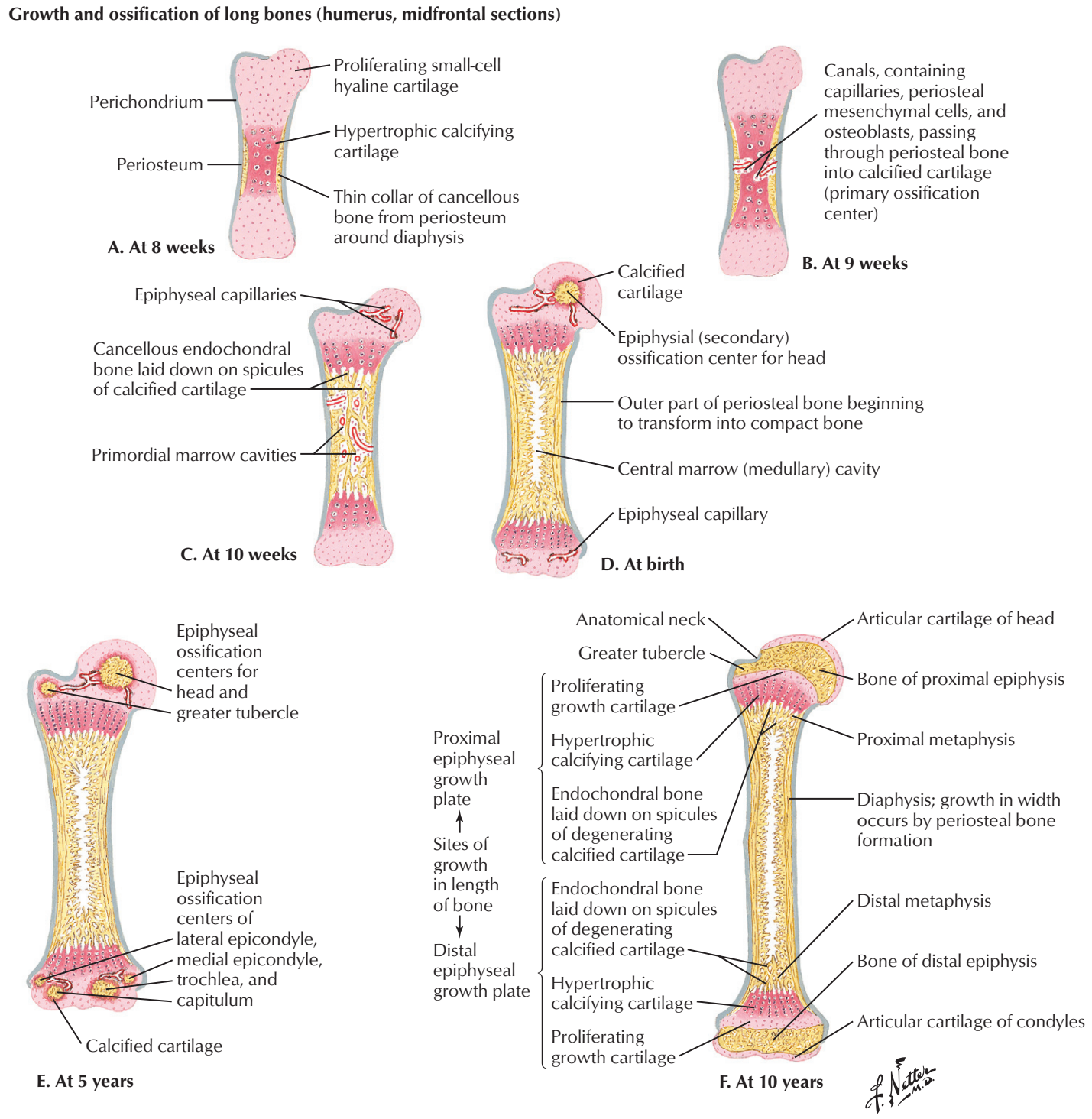


FIGURE 8.12 ENDOCHONDRAL OSSIFICATION IN A LONG BONE

Perichondrium differentiates into periosteum, and a **periosteal collar** of bone forms around the diaphysis (shaft). The cartilage becomes calcified in the center of the diaphysis; the cartilage cells hypertrophy and die, and the cartilage breaks up. Blood vessels invade the area, and osteoblasts begin to deposit bone on the remaining cartilage spicules as a **primary center of ossification.**

Bone replaces cartilage, and the ossification extends toward each end of the diaphysis. The process is repeated in the epiphyses as **secondary centers of ossification** appear. Bone fills the epiphyses except for cartilage on articular surfaces and the growth plate between the epiphysis and the diaphysis. The metaphysis is the flaring part of the bone near the growth plate.

Close-up view of developing epiphysis and epiphyseal growth plate

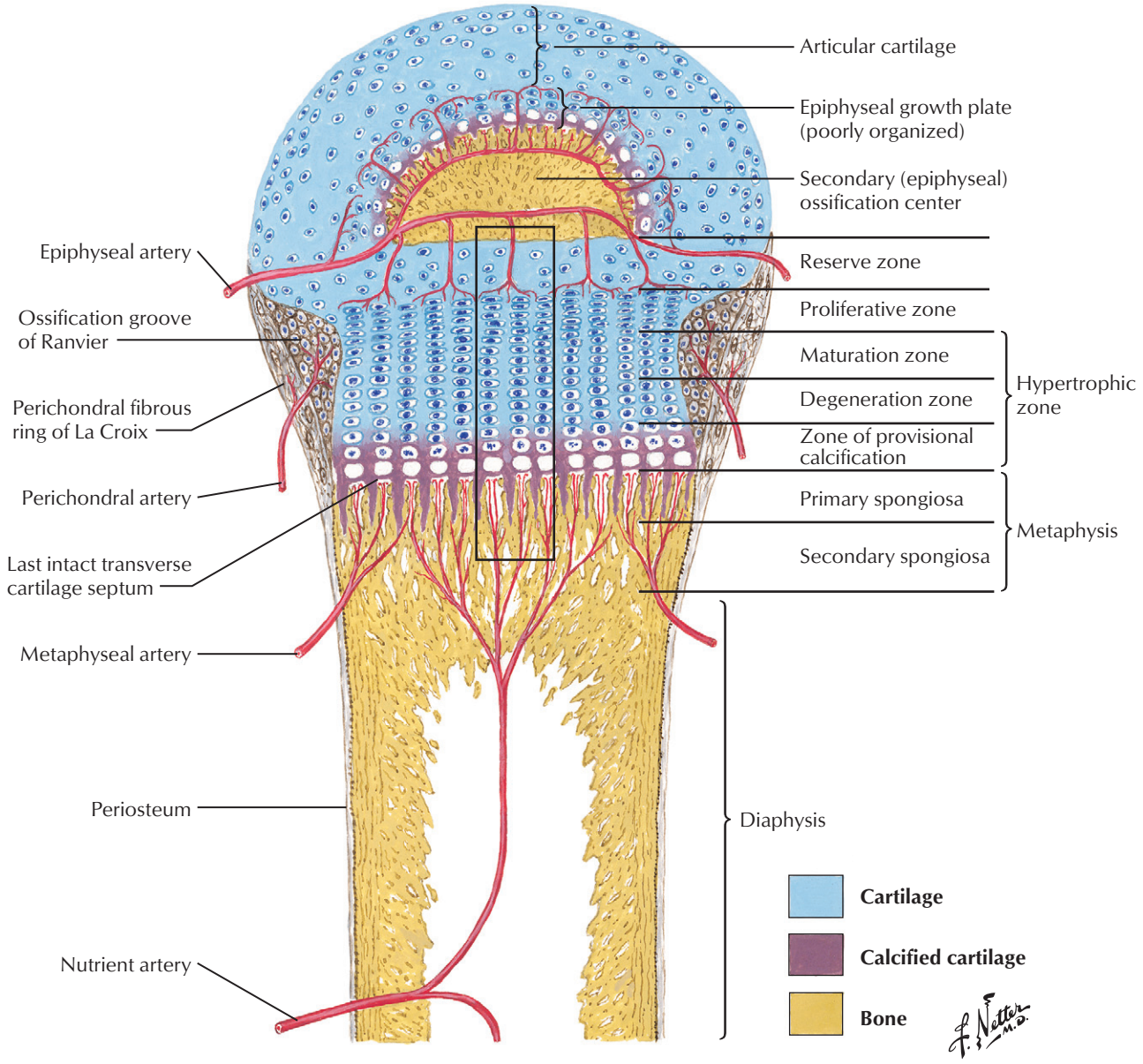
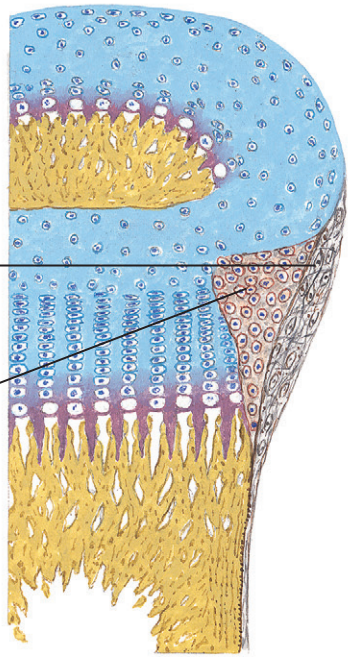
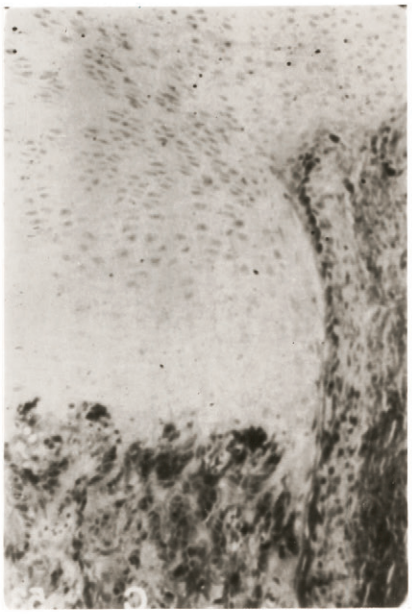


FIGURE 8.13 EPIPHYSEAL GROWTH PLATE

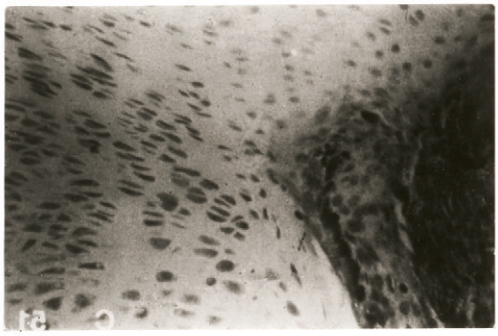
The **metaphysis** and bony portion of the growth plate are well supplied with blood, but only the uppermost portion of the cartilage cell columns (proliferative zone) is vascularized. The hypertrophic zone is avascular; cells are poorly oxygenated and nourished, and the lowermost cells degenerate and die. These vascular phenomena have profound physiological significance. Blood is present where new cartilage is added for growth in bone length at the epiphyseal end of the plate and where bone forms at the diaphyseal end. It is absent where cartilage needs to be eliminated.

Peripheral fibrocartilaginous element of growth plate





Microscopic section (H&E) corresponds generally to illustration at left



High-power section shows cells of ossification groove of Ranvier apparently "flowing" into cartilage at level of reserve zone, thus contributing to growth in width of growth plate. Note presence of arterioles (cut-in section)

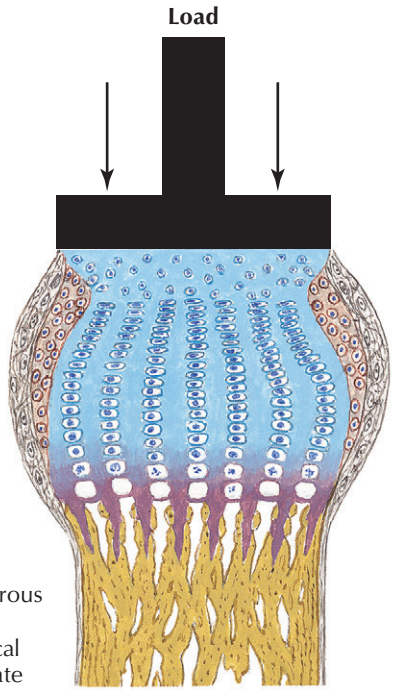


Illustration of how perichondral fibrous ring of La Croix acts as limiting membrane and provides mechanical support to cartilaginous growth plate

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FIGURE 8.14 PERIPHERAL CARTILAGE FUNCTION IN THE EPIPHYSIS

Cartilage is designed to withstand compressive forces. Cartilage at the periphery of the epiphyseal growth plate is not stratified into the zones of the plate. It is more homogeneous and contributes new cartilage for the growth in width of the plate. The perichondrium around it is more fibrous than is typical of perichondrium or periosteum to provide more support for the expansion of the epiphyseal plate that results from compressive forces.

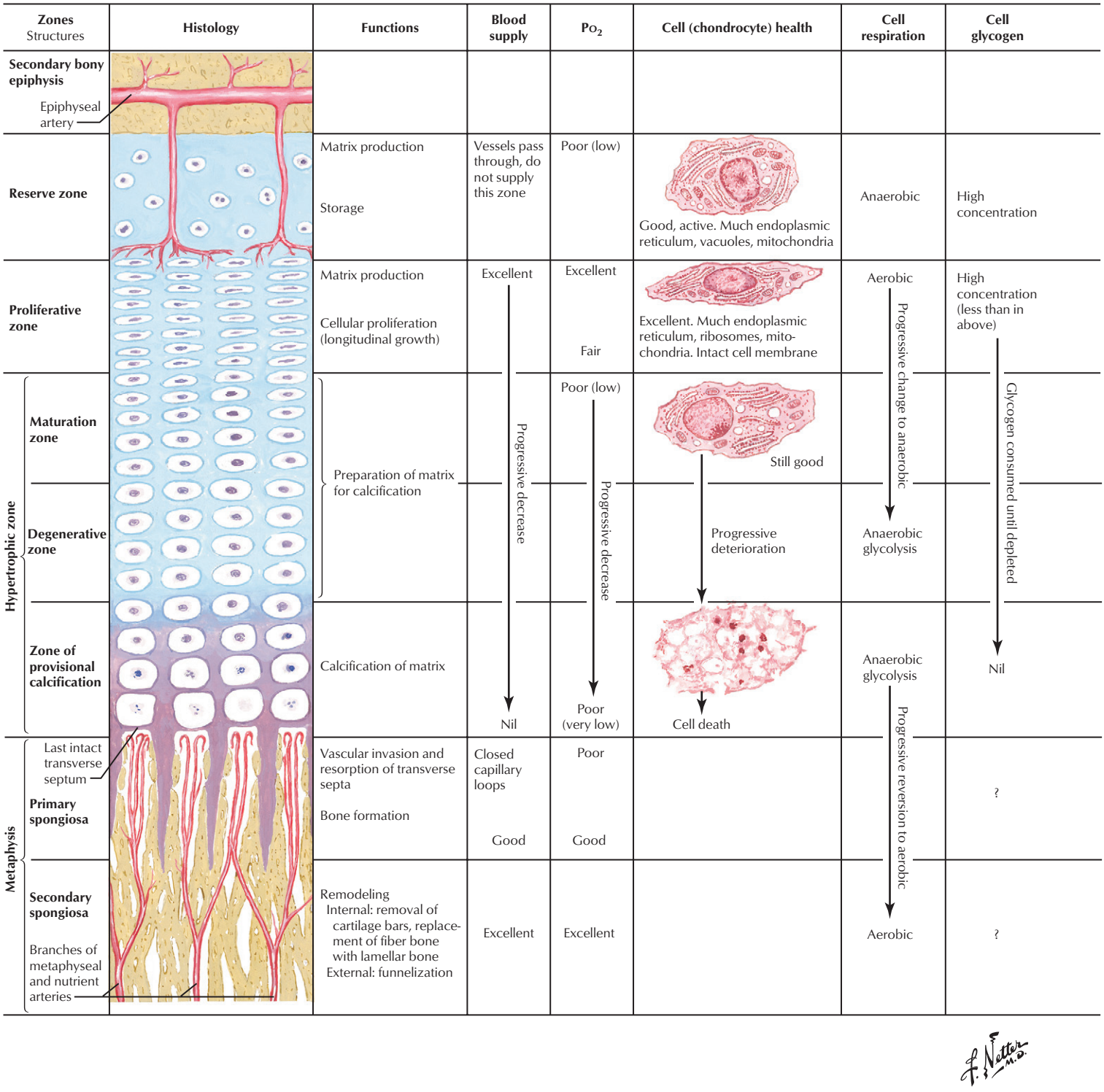


FIGURE 8.15 STRUCTURE AND FUNCTION OF THE GROWTH PLATE

The endochondral ossification process in the zones of the epiphyseal growth plate involves the same general steps that occur within the primary and secondary ossification centers. These include the calcification of cartilage matrix, the death of cartilage cells, the removal of cartilage, and bone deposition on remaining cartilage spicules. The primary difference is the production of new cartilage cells in the zone of proliferation. This is the ultimate source of new tissue for the growth in length of long bones.

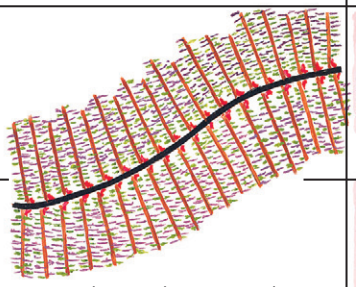
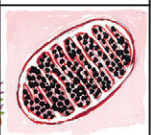
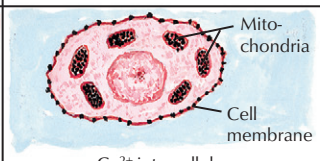
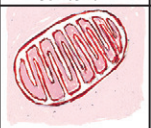
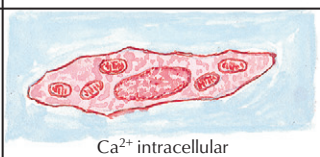
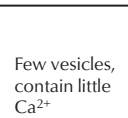
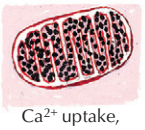
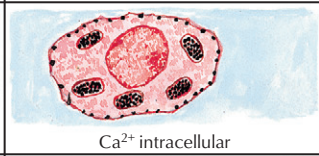
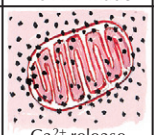
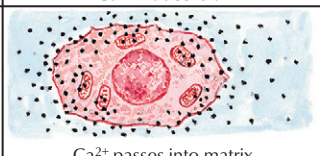
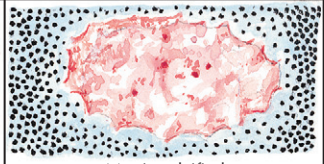
Proteoglycans in matrix	Mitochondrial activity	Matrix calcification	Matrix vesicles	Exemplary diseases	Defect (if known)
	 High Ca^{2+} content	 Ca^{2+} intracellular	 Few vesicles, contain little Ca^{2+}	Diastrophic dwarfism (also, defects in other zones) Pseudoachondroplasia (also, defects in other zones) Kniest's syndrome (also, defects in other zones)	Defective type II collagen synthesis Defective processing and transport of proteoglycans Defective processing of proteoglycans
	 ATP made	 Ca^{2+} intracellular	 Few vesicles, contain little Ca^{2+}	Gigantism Achondroplasia Hypochondroplasia Malnutrition, irradiation injury, glucocorticoid excess	Increased cell proliferation (growth hormone increased) Deficiency of cell proliferation Less severe deficiency of cell proliferation Decreased cell proliferation and/or matrix synthesis
Aggregated proteoglycans (neutral mucopolysaccharides) inhibit calcification					
Progressively disaggregated	 Ca^{2+} uptake, no ATP made	 Ca^{2+} intracellular	 Contain little Ca^{2+}	Mucopolysaccharidosis (Morquio's syndrome, Hurler's syndrome)	Deficiencies of specific lysosomal acid hydrolases, with lysosomal storage of mucopolysaccharides
	 Ca^{2+} release begins	 Ca^{2+} passes into matrix	 Begin Ca^{2+} uptake		
 Disaggregated proteoglycans (acid mucopolysaccharides) permit calcification	 Ca^{2+} released	 Matrix calcified	 Crystals in and on vesicles	Rickets, osteomalacia (also, defects in metaphysis)	Insufficiency of Ca^{2+} and/or P_i for normal calcification of matrix
				Metaphyseal chondrodysplasia (Jansen and Schmid types) Acute hematogenous osteomyelitis	Extension of hypertrophic cells into metaphysis Flourishing of bacteria due to sluggish circulation, low Po_2, reticuloendothelial deficiency
				Osteopetrosis Osteogenesis imperfecta Scurvy Metaphyseal dysplasia (Pyle's disease)	Abnormality of osteoclasts (internal remodeling) Abnormality of osteoblasts and collagen synthesis Inadequate collagen formation Abnormality of funnelization (external remodeling)

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FIGURE 8.16 PATHOPHYSIOLOGY OF THE GROWTH PLATE

Diseases that affect stature (either dwarfism or gigantism) are the result of abnormal processes in the zone of proliferation, such as increased or decreased cartilage cell proliferation. Abnormalities of bone tissue (e.g., rickets, osteomalacia, osteogenesis imperfecta, scurvy) originate in the metaphysis where bone forms in the epiphyseal plate. Any disruption of growth results in a diminished production of cartilage cells, but ossification is less affected and there is a resulting increase in bone density. These dense lines (Harris lines or lines of arrested growth) can be seen near the epiphyses in an x-ray of an adult bone as a record of acute trauma or insult during the growth period.

Skeleton of full-term newborn
Time of appearance of ossification centers (primary unless otherwise indicated)

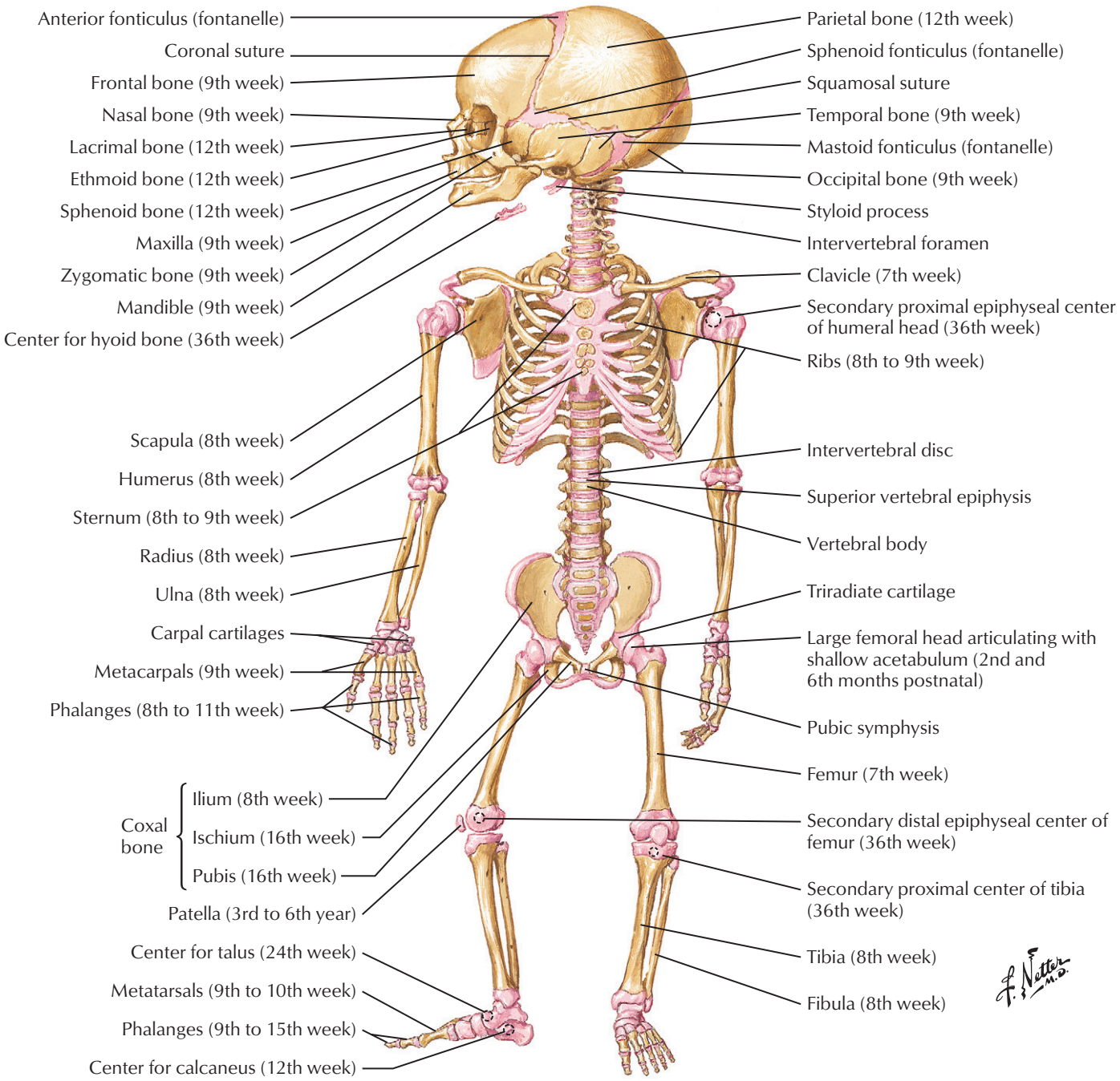


FIGURE 8.17 OSSIFICATION IN THE NEWBORN SKELETON

Most fetal bone is woven bone. Lamellae and osteons form with the postnatal increase in size of the skeleton. The diaphyses are mostly ossified at birth, and the secondary centers are just beginning to appear. The epiphyseal growth plates persist through the adolescent years. Once they have ossified, growth in the length of the bones (and the stature of an individual) can no longer occur.

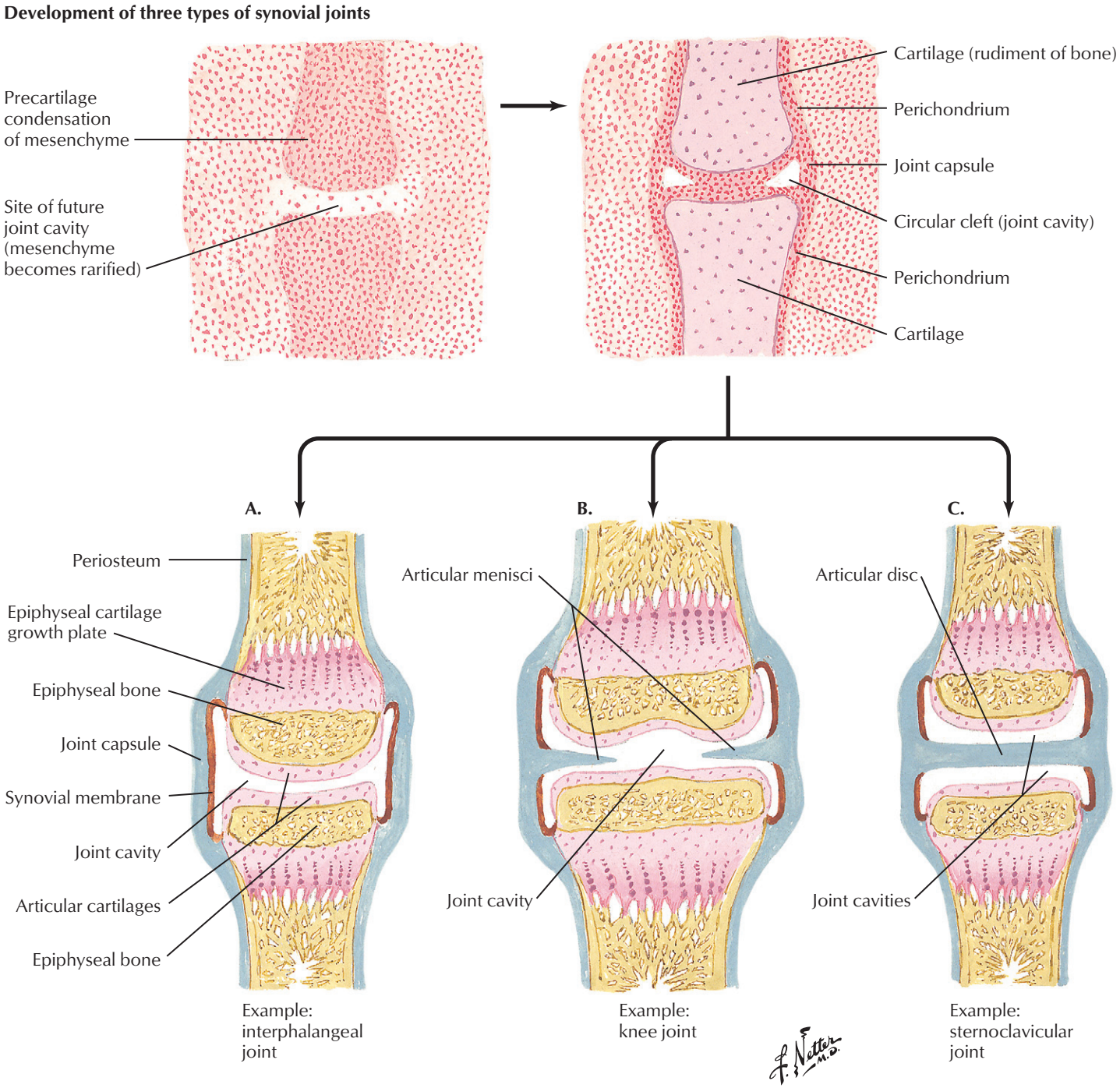


FIGURE 8.18 JOINT DEVELOPMENT

The classification of joints is based on the fate of the mesenchyme between the early bony precursors. **Cartilaginous joints (synchondroses)** are designed to withstand compressive forces and have hyaline cartilage connecting the bony elements (e.g., spheno-occipital synchondrosis and epiphyseal plates). Dense connective tissue unites the bones in **fibrous joints.** The fibrous joints of the neurocranium resist tensile forces from the growing brain. **Synovial joints** have a joint cavity designed for movement and may have an articular disc. The mesenchyme disappears, and hyaline cartilage caps the articular ends of the bones. Synovial joints are the most common of the three types.

Differentiation of somites into myotomes, sclerotomes, and dermatomes

Cross section of human embryos

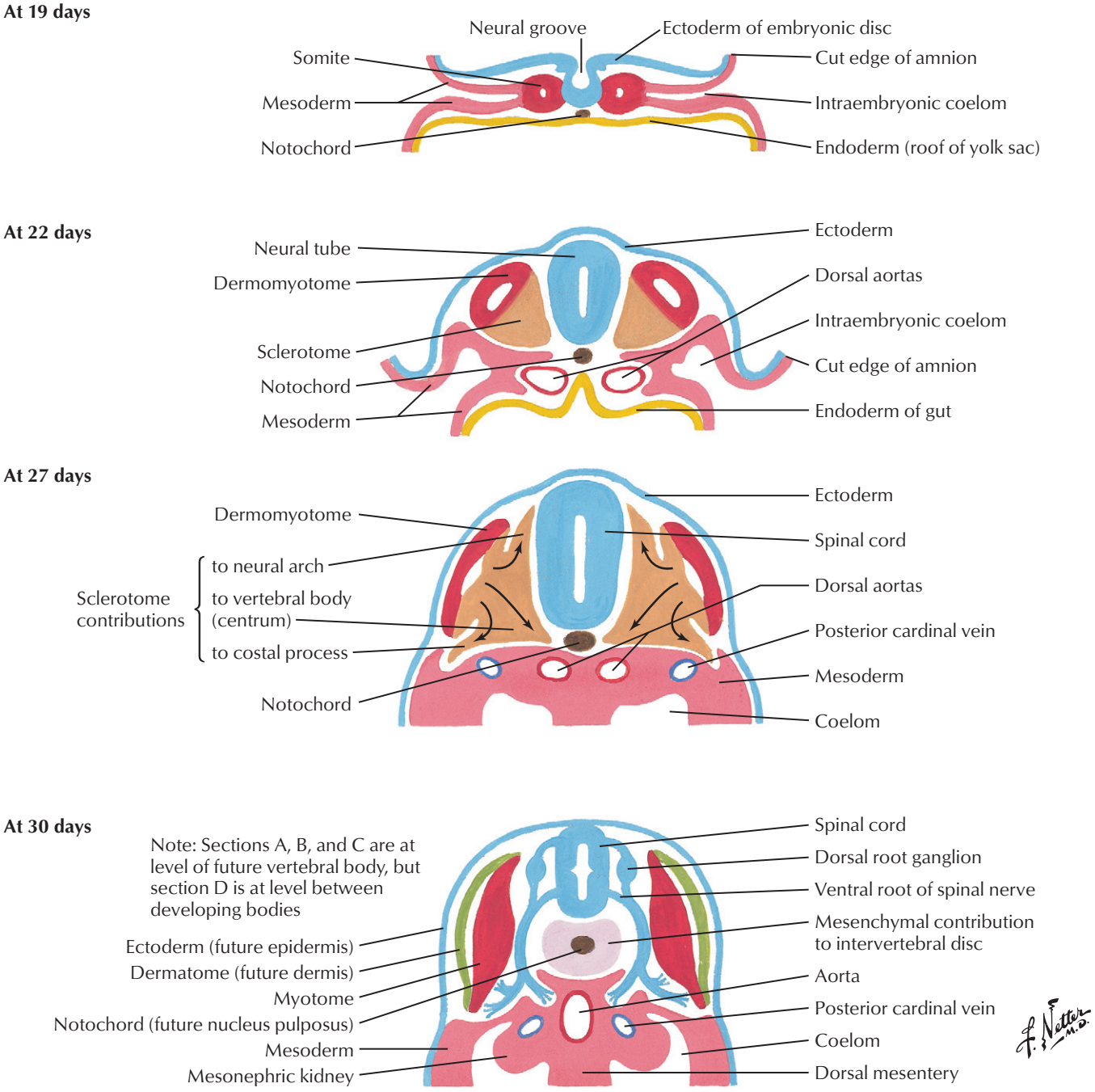


FIGURE 8.19 MUSCULAR SYSTEM: PRIMORDIA

Skeletal (striated) muscles develop from the myotome of somites and somatopleure mesoderm. Myotomes give rise to the muscles of the trunk and some muscles in the head. Muscle cells of the limbs are derived from migrating myotome cells, whereas the connective tissue elements of muscle—tendons, endomysium, perimysium, and epimysium—come from somatopleure mesenchyme of the limbs. Mesoderm of somatopleure can also differentiate into muscle, as it appears to do in the ventral trunk region.

Segmental distribution of myotomes in fetus of 6 weeks

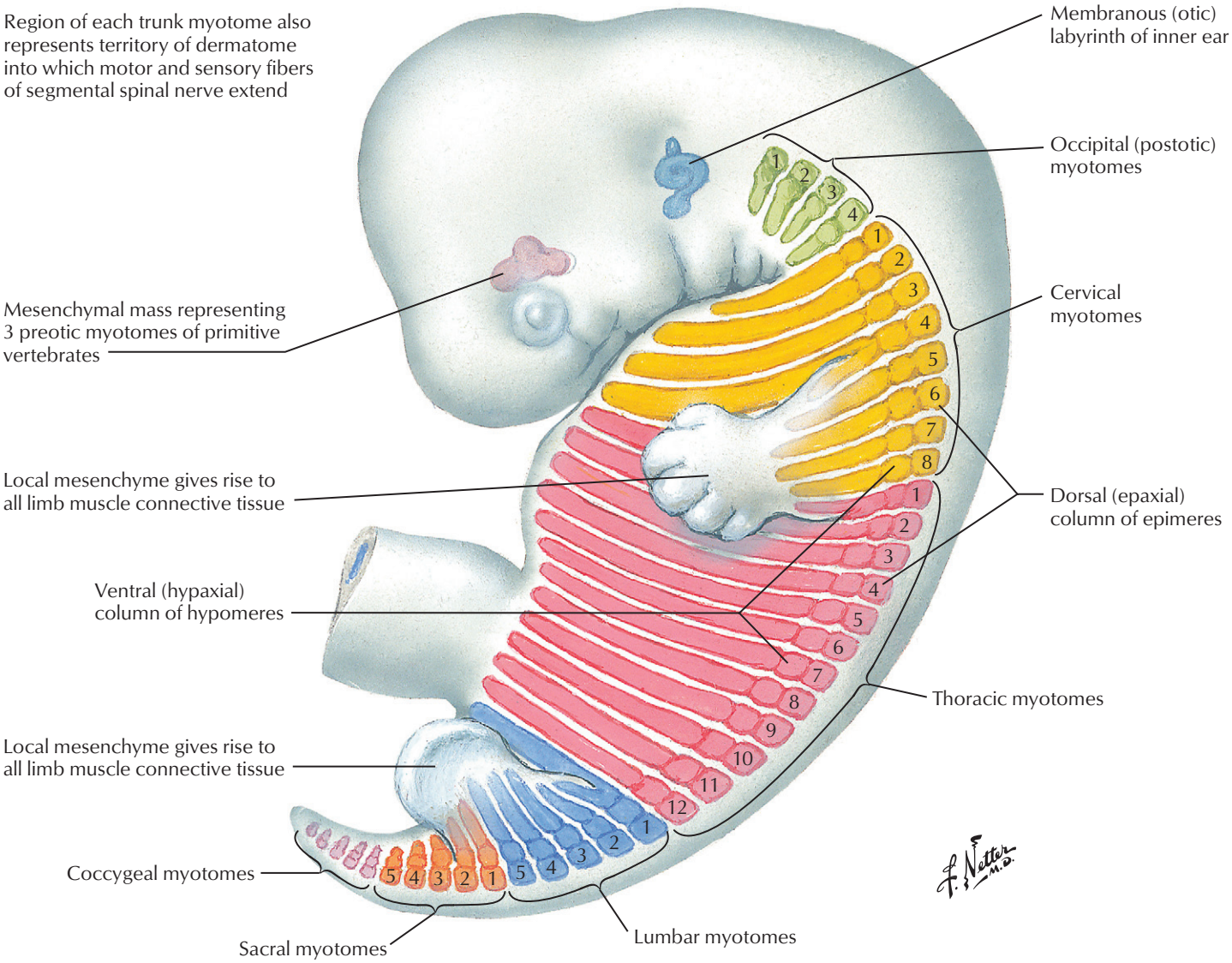
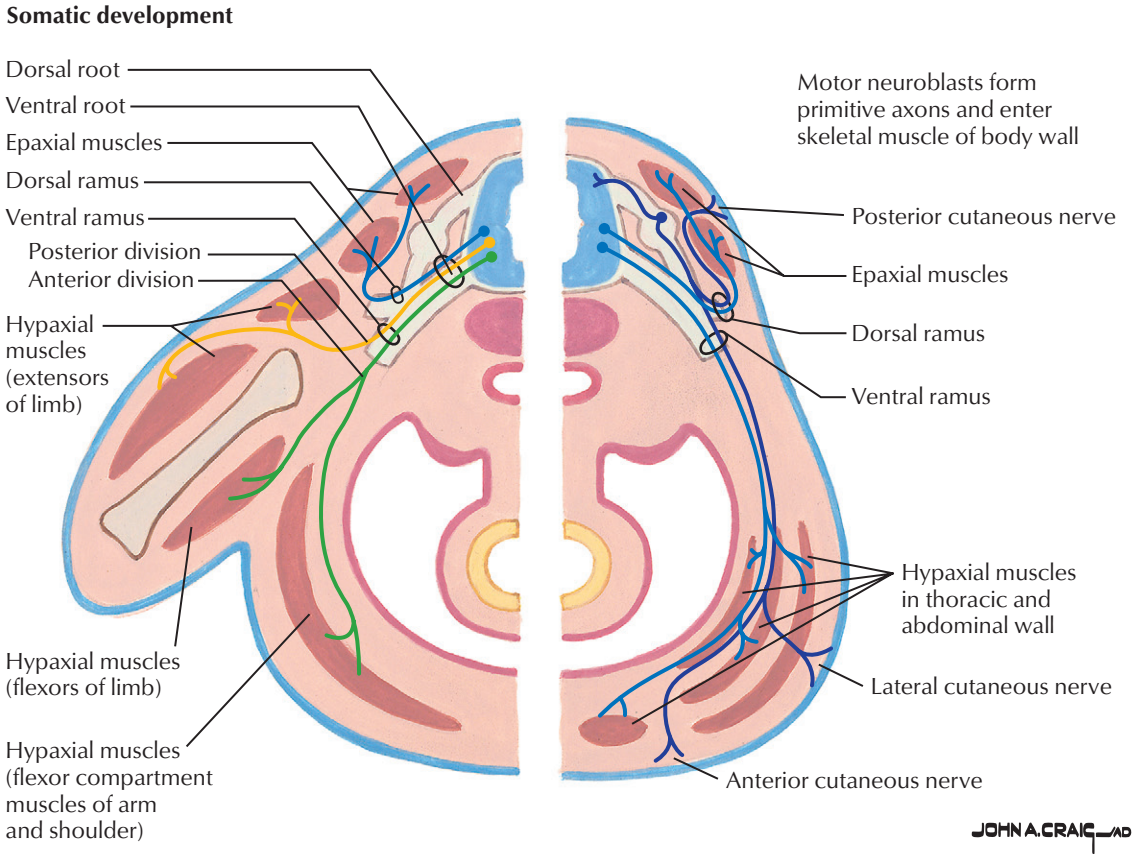


FIGURE 8.20 SEGMENTATION AND DIVISION OF MYOTOMES

Like the somites from which they are derived, the myotomes have a segmental distribution in the embryo, and each segment is innervated by a spinal nerve (cervical, thoracic, lumbar, or sacral). The myotomes begin to divide into a small, dorsal segment called an **epimere,** and a larger ventral segment called the **hypomere.** Adjacent myotomes fuse to form individual skeletal muscles, so most muscles are innervated by more than one spinal segment (e.g., C3, C4, and C5). This occurs by innervation from multiple spinal nerves (back and abdominal muscles of the trunk) or the joining of multiple spinal segments into single nerves in the brachial and lumbosacral plexuses for limb muscle innervation.



Innervation of somatopleure (body wall) derivatives by the somatic nervous system (spinal nerves). On the left is the organization of motor innervation to the back *(blue neurons)* and limbs *(yellow and green neurons)*. On the right is motor innervation to trunk muscles and sensory innervation in cutaneous nerves. Sensory nerve processes are found in all nerves to muscle in addition to cutaneous nerves. Sympathetic fibers supplying arterial smooth muscle are also in every spinal nerve branch.

FIGURE 8.21 EPIMERE, HYPOMERE, AND MUSCLE GROUPS

The **epimere** of a myotome is innervated by the **dorsal primary ramus** of a spinal nerve (*blue motor neurons on the left, above*) and gives rise to the **intrinsic back muscles** (the spinotransverse [splenius] group, the erector spinae, and the transversospinalis group). The **hypomere** is supplied by the **ventral primary ramus** of a spinal nerve. The lateral and ventral muscles of the trunk and all of the muscle cells of the limbs come from hypomeres, which further divide in the limbs into ventral, **flexor compartment muscle groups** and dorsal, **extensor compartment muscle groups.** The flexors are innervated by **anterior division branches** of ventral rami (*green motor neurons on the left, above*) in the brachial plexus and lumbosacral plexus, the extensors by **posterior divisions** of ventral rami (*yellow neurons*). All nerves supplying muscles contain sensory (and sympathetic) neurons.

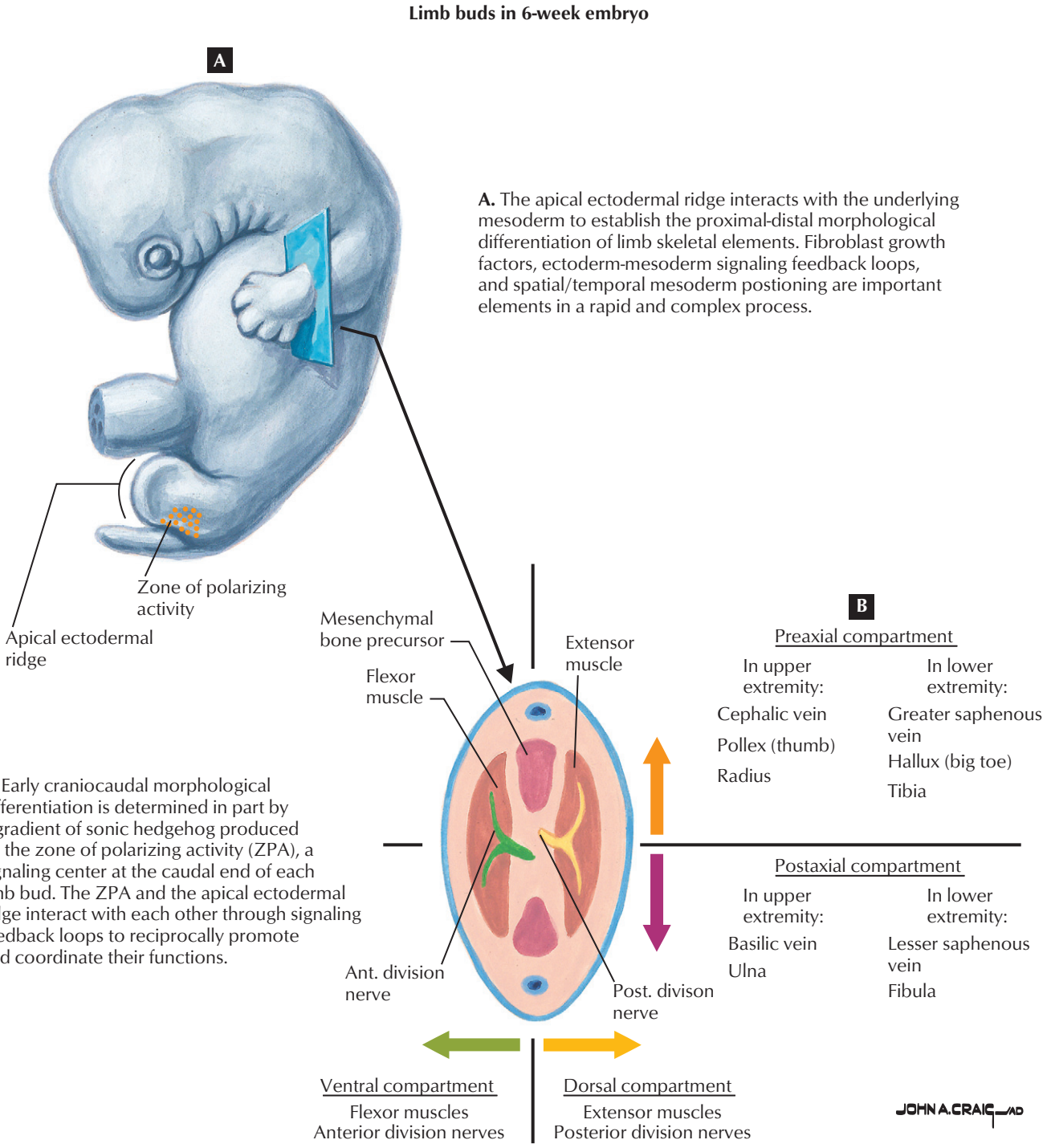
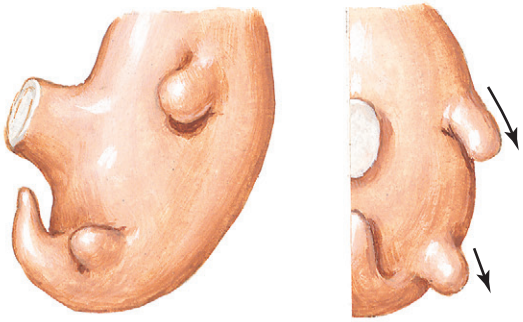


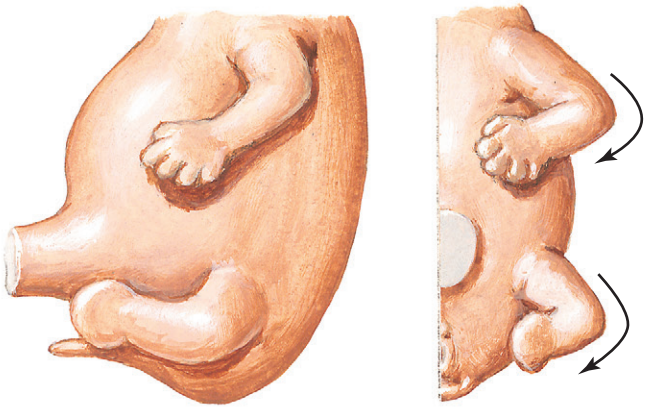
FIGURE 8.22 DEVELOPMENT AND ORGANIZATION OF LIMB BUDS

Limb buds develop as paddle-like extensions of the ventrolateral body wall. They contain somatopleure mesenchyme capped by an **apical ectodermal ridge (AER).** Hypomere cells from somite myotomes migrate into the buds to form muscle cells. The connective tissue of muscle comes from somatopleure mesenchyme. Limb bud organization is based on transverse and dorsoventral planes. The cranial half of a limb bud is the **preaxial compartment;** the caudal half is the **postaxial compartment.** More functionally important, the buds are divided into a ventral, **flexor compartment** and dorsal, **extensor compartment.** Signals from somites trigger limb bud formation. See page 14 for the roles of various growth factors in development of the limb. While their actions seem straightforward, the control of their expression is complicated.

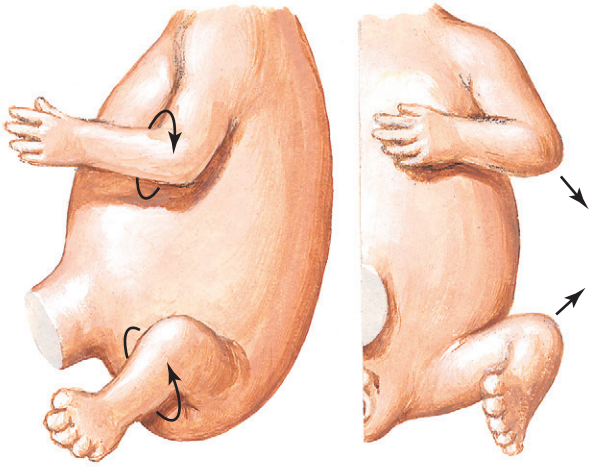
Changes in position of limbs before birth



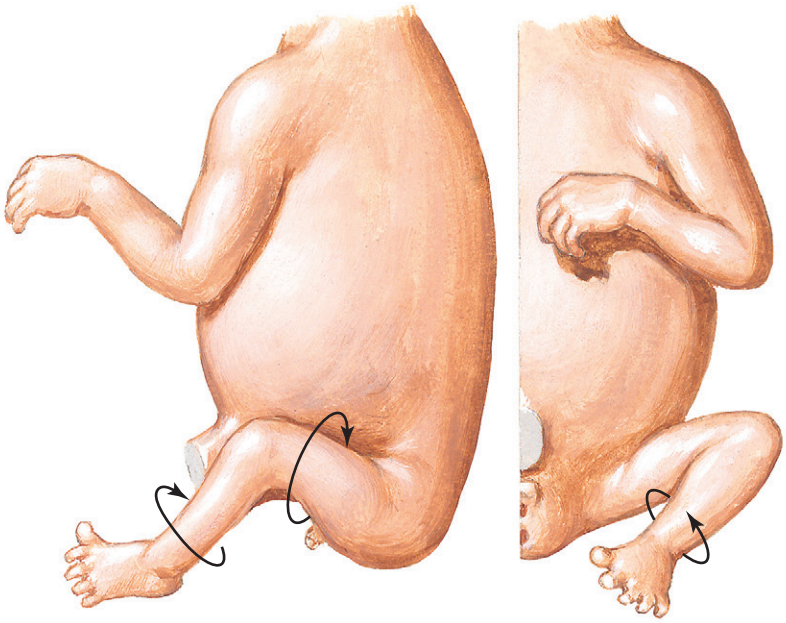
At 5 weeks. Upper and lower limbs have formed as finlike appendages pointing laterally and caudally



At 6 weeks. Limbs bend anteriorly, so elbows and knees point laterally, palms and soles face trunk



At 7 weeks. Upper and lower limbs have undergone 90-degree torsion about their long axes, but in opposite directions, so elbows point caudally and knees cranially



At 8 weeks. Torsion of lower limbs results in twisted or "barber pole" arrangement of their cutaneous innervation

FIGURE 8.23 ROTATION OF THE LIMBS

The limb buds are first oriented with their ventral surfaces facing medially and dorsal surfaces facing laterally. *Dorsal* and *ventral* in early limbs do not refer to adult anatomical directions but rather to continuity with the ventral and dorsal surfaces of the embryonic trunk. The upper extremity rotates 90 degrees laterally so that the ventral, flexor compartment faces anteriorly. The lower extremity rotates 90 degrees medially so that the embryonic ventral, flexor compartment is *posterior* in the lower limb and the extensors are in front. The rotation occurs as a torsion in the femoral (and humeral) shaft. The flexors and extensors of the hip are mostly unaffected: Hip flexors are anterior; extensors are posterior.

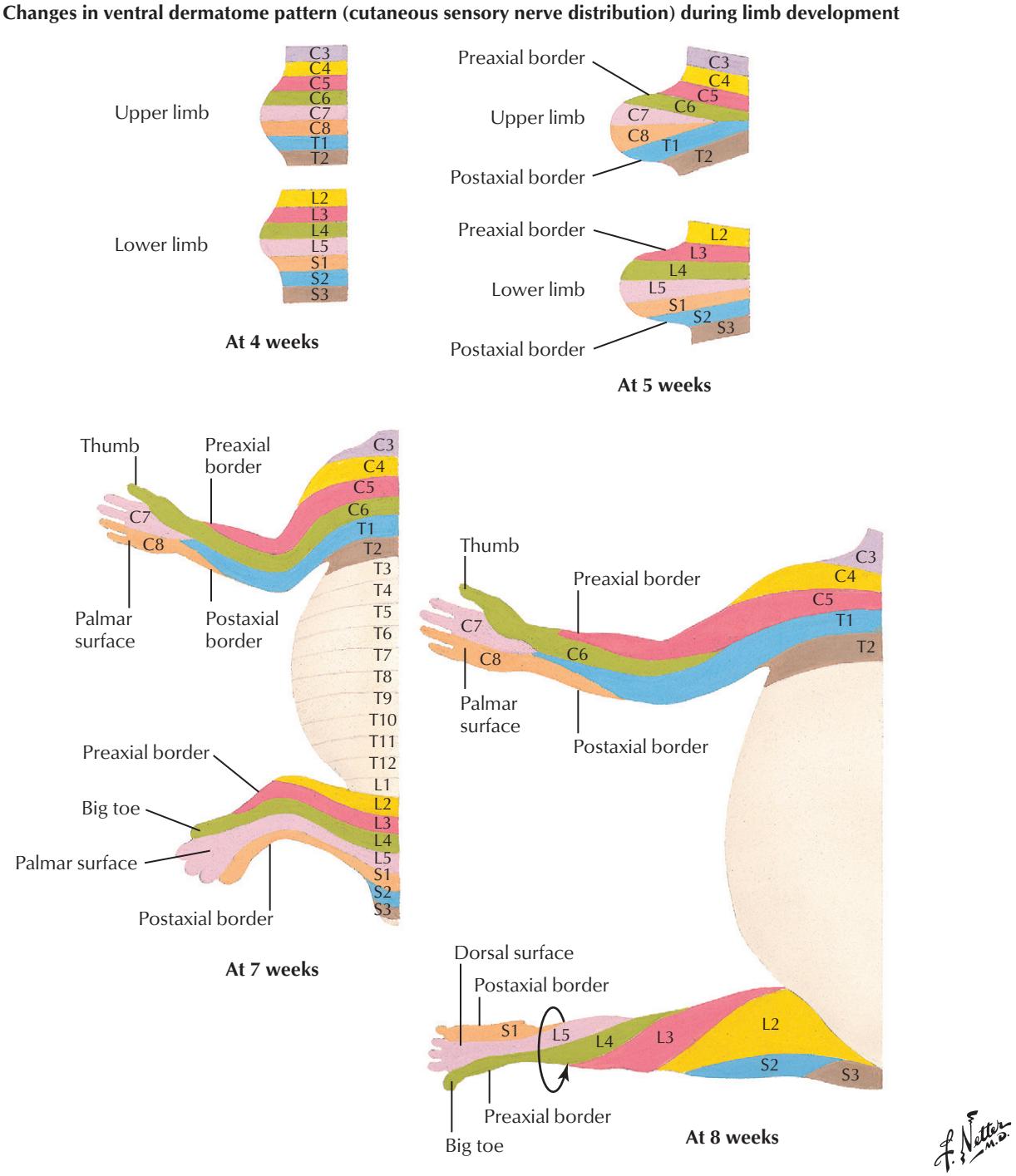


FIGURE 8.24 LIMB ROTATION AND DERMATOMES

Rotation of the lower limb results in a reversal of the preaxial and postaxial borders and a spiral, or "barber pole," arrangement of dermatomes. Spinal nerve segments on the anterior surface of the lower extremity extend medially and inferiorly, and the big toe (hallux) gets a higher dermatome (L4) than the little toe (S1). The lower extremity is an extension of the trunk, and the lowest dermatomes (sacral and coccygeal) are in the perineum, not the foot.

Comparison of embryonic limb organization to the plan of the brachial plexus

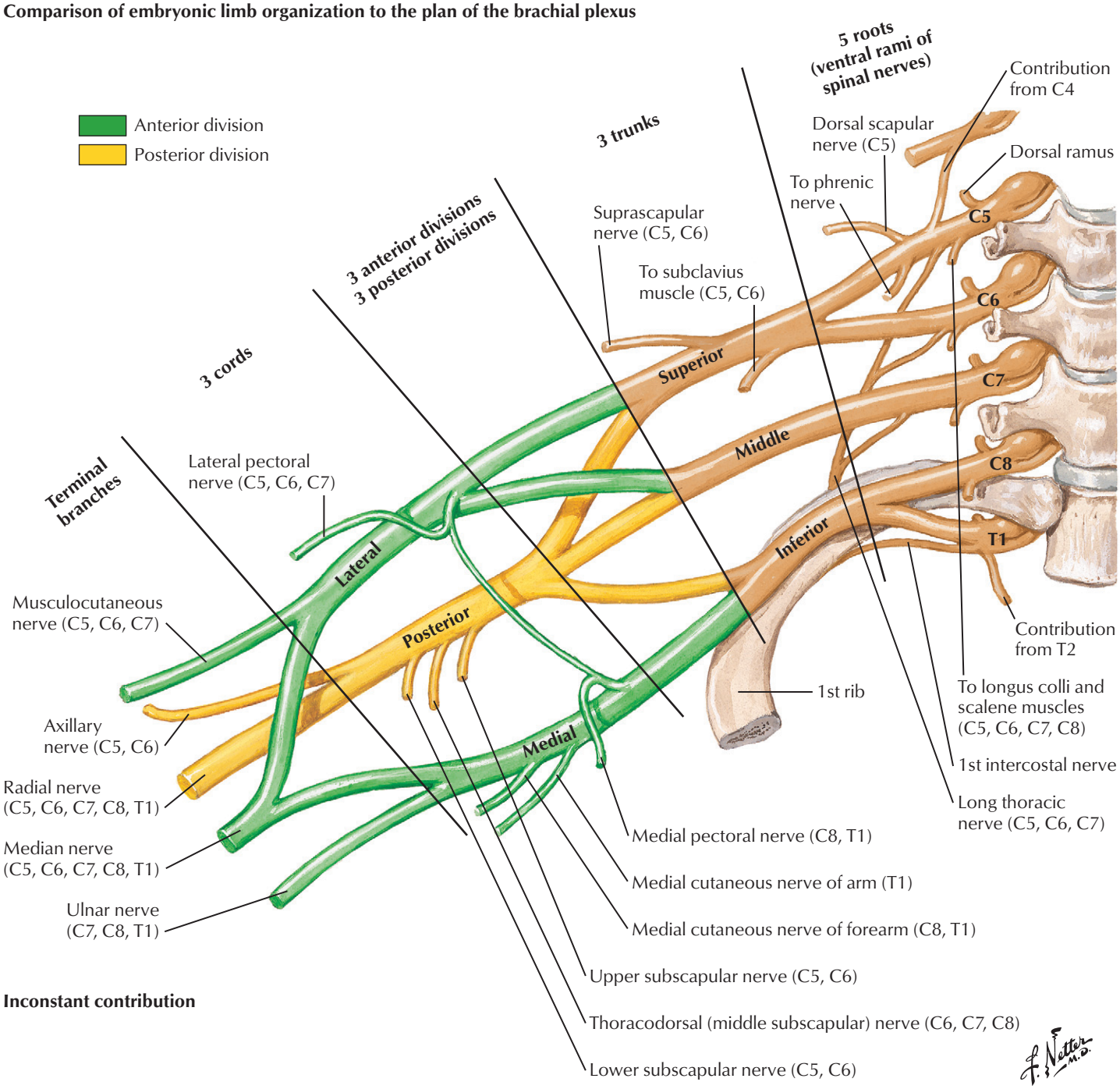


FIGURE 8.25 EMBRYONIC PLAN OF THE BRACHIAL PLEXUS

The separation of the ventral rami and nerve trunks into anterior and posterior divisions is the most functionally important component of the brachial plexus. This relates to the embryonic separation of the myotome hypomeres into flexor and extensor compartment muscle groups. Nerve branches of anterior divisions (musculocutaneous, median, ulnar) go to flexor compartment muscles; branches of posterior divisions (axillary, radial, thoracodorsal, subscapular) supply extensor compartment muscles.

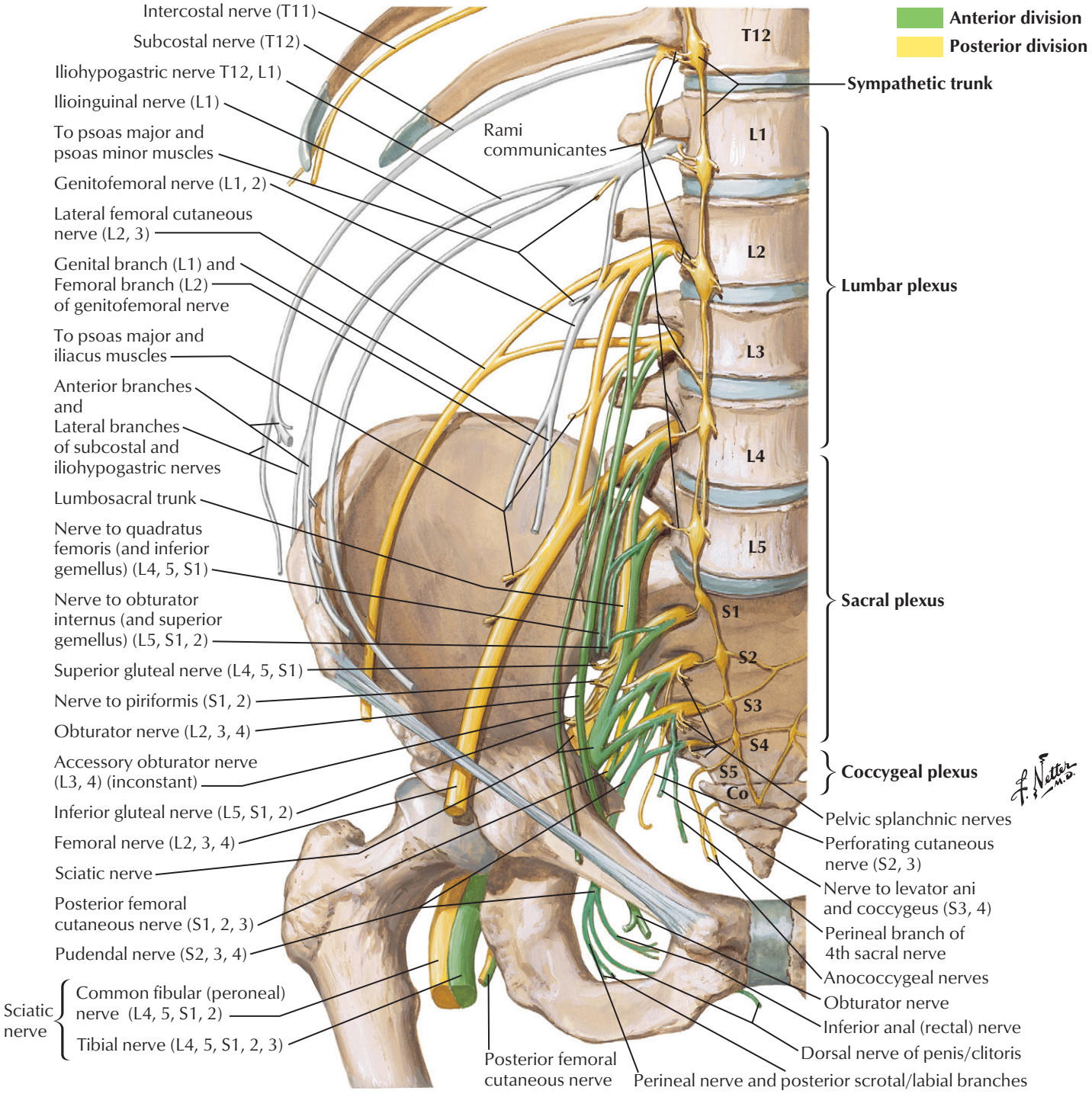


FIGURE 8.26 DIVISIONS OF THE LUMBOSACRAL PLEXUS

Anterior division nerves (tibial, obturator) to flexors are on the posterior aspect of the lower extremity, medial thigh, and sole of the foot. Posterior division nerves (femoral, common fibular) for extensors are mostly anterior in the adult.

Developing skeletal muscles at 8 weeks (superficial exposure)

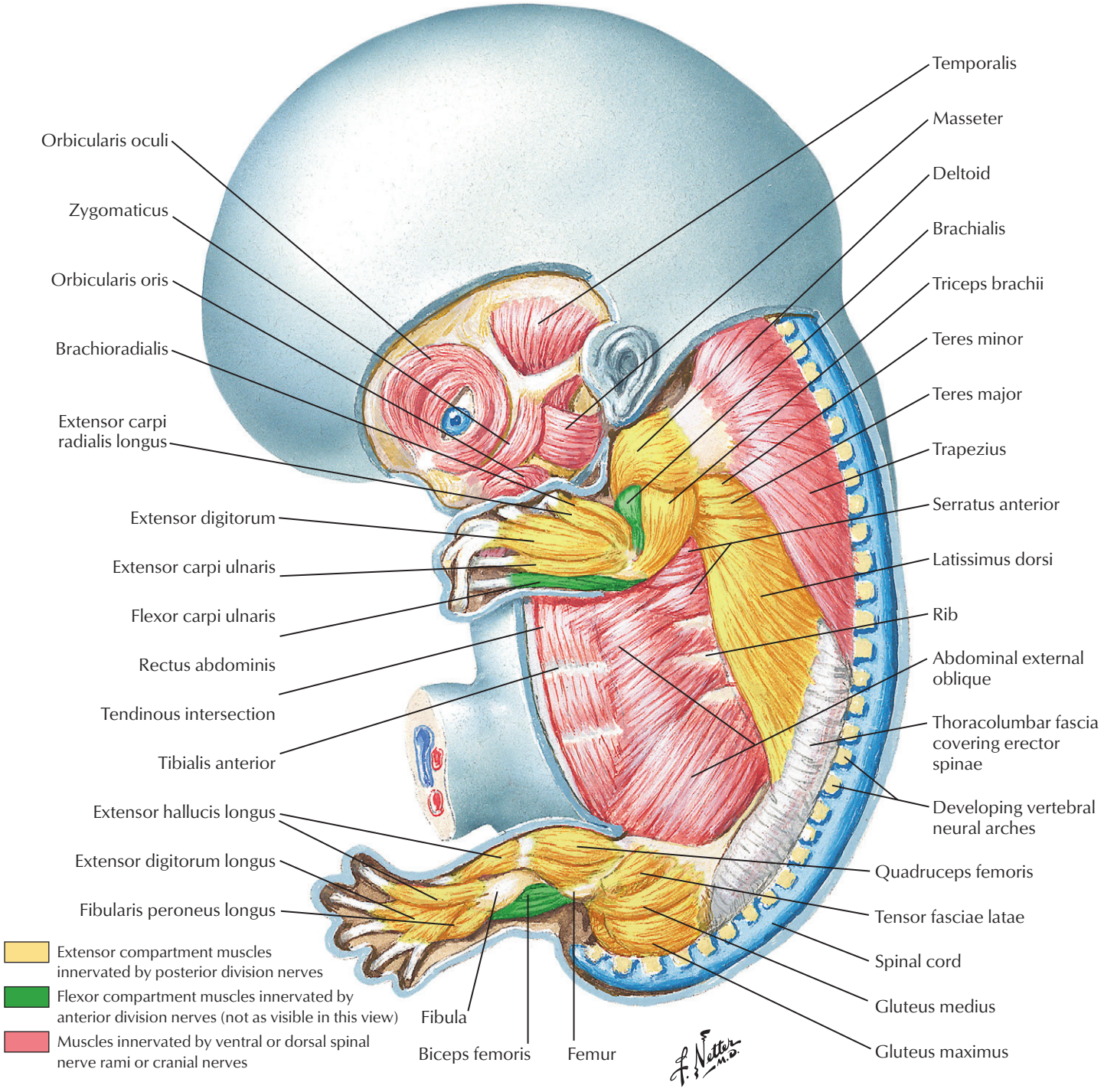


FIGURE 8.27 DEVELOPING SKELETAL MUSCLES

Muscles of the head and neck are derived from somitomeres, some (extraocular eye muscles and tongue muscles) directly, and the rest (muscles of mastication and facial expression, and neck and larynx muscles) via somitic cell migration into the pharyngeal arches. Intercostal and abdominal muscles are innervated by the ventral rami of spinal nerves, and the limbs are innervated by the separation of the ventral rami into anterior and posterior division nerves of the brachial plexus and lumbosacral plexus. Most of the flexor muscles are not visible in the figure because the flexor compartments are in the medial, ventral half of the limb buds. The ventral surface of the limb buds are continuous with the ventral surface of the trunk.

Terminology

Axial skeleton	The skeleton along the vertical axis of the body: the skull, vertebral column, and ribs.
Apical ectodermal ridge	A ridge of ectoderm at the distal margin of the limb buds that plays an important signaling role in the determination of proximal-distal morphological differentiation of the limb bones.
Appendicular skeleton	(L., appendix—"appendage") Limb bones, including anchoring girdle bones—the clavicle, scapula, and pelvis.
Cancellous bone	Spongy or trabecular bone that forms the interior of most bones.
Cement line	Thin line surrounding osteons consisting of highly mineralized bone lacking collagen fibers.
Cranium	Skull, except the mandible.
Diaphysis	Shaft of a long bone formed by a primary center of ossification.
Diploë	Cancellous bone between inner and outer layers of compact bone in the flat neurocranial bones.
Endochondral bone	Bones that begin with a hyaline cartilaginous model. Includes most of the postcranial bones and the cranial base at the interface between the neurocranium (braincase) and viscerocranium (facial skeleton).
Endomysium	Thin, connective tissue layer surrounding each skeletal muscle cell.
Endosteum	Equivalent of periosteum on the inside of the wall of compact bone.
Epimere	Dorsal part of a somite myotome that forms the intrinsic back muscles and is innervated by the dorsal rami of spinal nerves.
Epimysium	Dense connective tissue enveloping a muscle.
Epiphysis	The ends of long bones formed from secondary centers of ossification.
Fiber	A muscle cell or a nerve cell.
Filaments	Threads of actin and myosin molecules within muscle cells.
Hyaline cartilage	Most common type of cartilage; it has a homogeneous matrix and is found in ribs, most of the larynx, rings of the airway, articular cartilage, and epiphyseal plates. The other two types of cartilage, elastic cartilage and fibrocartilage, are classified by the type of fibers imbedded in the cartilage matrix.
Hypomere	Ventral part of a somite myotome that forms all muscles other than intrinsic back muscles (intercostal and abdominal muscles, and all muscle cells in the limbs). Hypomeres are innervated by the ventral rami of spinal nerves.
Interstitial growth	Addition of new cells and connective tissue matrix from within the matrix. Cartilage grows interstitially; bone does not.
Lacunae	(L., "little lakes") Spaces in bone matrix where osteocytes reside. Bone cells in lacunae are osteocytes. Cells on bone surface are osteoblasts.
Lamellae	Layers of bone in mature, compact bone. Organized as circumferential lamellae, concentric lamellae of osteons, and interstitial lamellae between osteons. Separated by thin layers of collagen fibers that are parallel within layers and perpendicular between layers.

Terminology, cont'd

Metaphysis	Flaring ends of a long bone under the epiphyseal growth plates where new bone is deposited with the growth in length of the bone.
Neurocranium	Bones surrounding the brain. The bottom of the neurocranium is the cranial base at the interface between neurocranium and viscerocranium.
Osteoid	Organic component of bone matrix that is deposited by osteblasts before it becomes mineralized by membrane-bound packets of hydroxyapatite crystals.
Osteon	A haversian system, the structural unit of mature, compact bone consisting of a series of concentric lamellae surrounding a central (haversian) canal containing an arteriole, nerve, and other cells.
Perimysium	Connective tissue surrounding groups of skeletal muscle cells or larger units within a muscle. It has epithelial, contractile, and connective tissue properties.
Periosteum	Outer fibrous covering of bones with an outer, dense connective tissue layer and inner osteogenic layer.
Plexus	(L., "braid") Interconnecting nerves or vessels.
Postcranial	Below the cranium. Postcranial skeleton consists of all bones except the skull.
Sclerotome	(G., "hard cutting") Ventromedial part of a somite that forms the endochondral bone of the vertebral column, ribs, and cranial base.
Skull	Cranium plus the mandible.
Trabeculae	(L., "little beams") Interconnecting bony spicules of spongy (or cancellous or trabecular) bone.
Viscerocranium	Facial skeleton consisting of the upper and lower jaws, nasal bones, and bony eye sockets.
Woven bone	Immature, nonlamellar bone where the collagen fibers are in a random, "woven" orientation in the matrix. Bone is always deposited as woven bone; most of the embryonic and fetal skeleton is woven bone.
Zone of polarizing activity	A signaling center at the caudal end of each limb bud that plays important roles in determining cranio-caudal differentiation of the limbs and interaction with the apical ectodermal ridge.

CHAPTER 9

HEAD AND NECK

MESODERMAL PRIMORDIA

Postotic somites, preotic somitomeres, head mesenchyme from neural crest, pharyngeal arch mesenchyme (from neural crest and somitomeres).

ECTODERMAL PRIMORDIA

Surface ectoderm, lining of the stomodeum (primitive oral cavity), pharyngeal grooves between the pharyngeal arches, and surface placodes.

ENDODERMAL PRIMORDIA

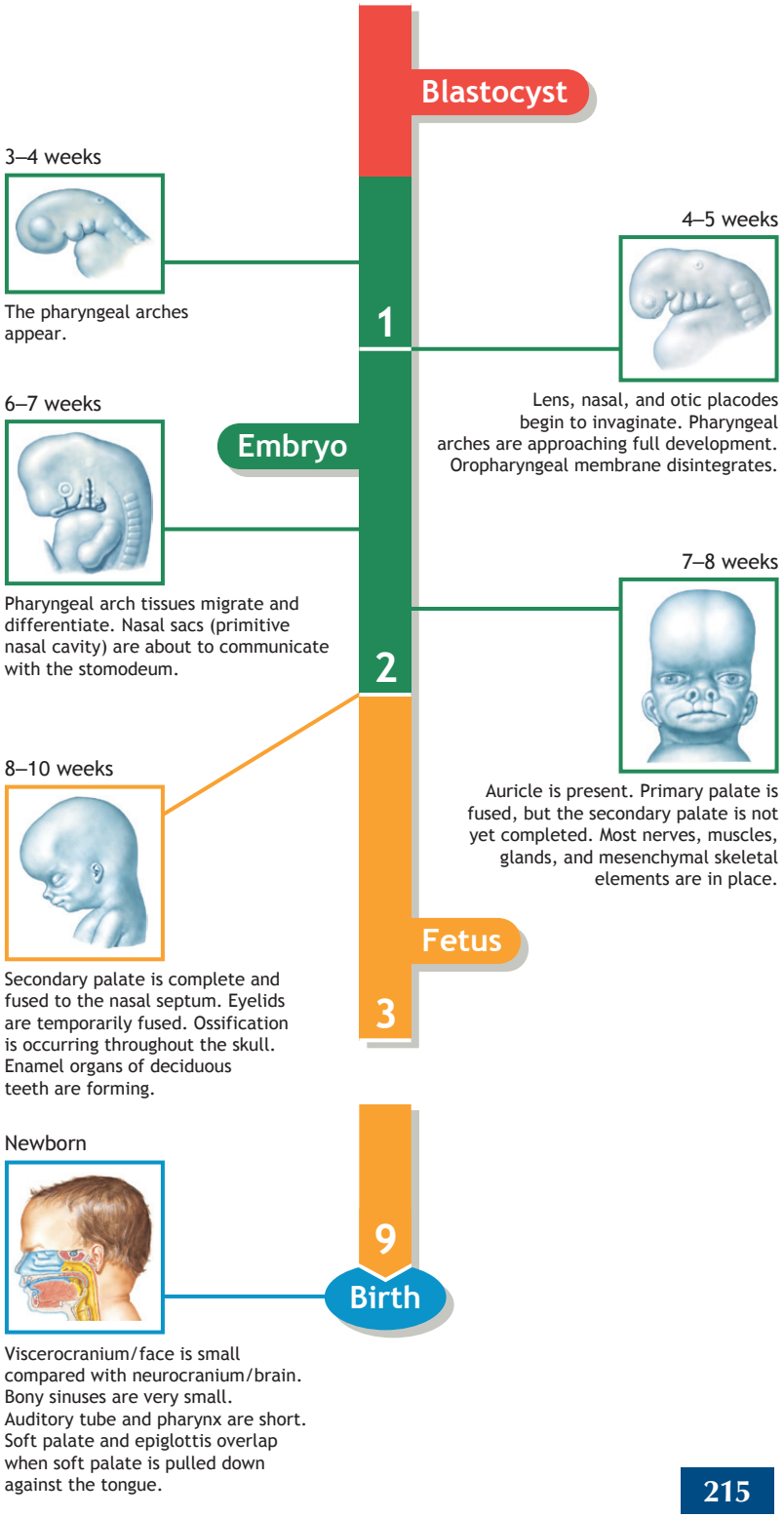
Foregut, pharyngeal pouches between the pharyngeal arches.

PLAN

The head and neck have segmental motor and sensory innervation like the rest of the body, but there are a number of new features. The head region is underdeveloped at the time of gastrulation, and little primitive streak mesoderm other than somitomeres extends into the head. The neural crest is the origin of most head mesenchyme, and much of it is organized into a series of horizontal bars flanking the foregut. These pharyngeal arches evolved as the gill apparatus in fish, but form most of the structures in the head and neck of higher animals. The head also has special sensory organs and related neurons that derive from ectodermal surface placodes. Even the predominant type of ossification in the head—intramembranous—is different than the endochondral bone formation in the postcranial skeleton.

TIMELINE

Prenatal Time Scale (Months)



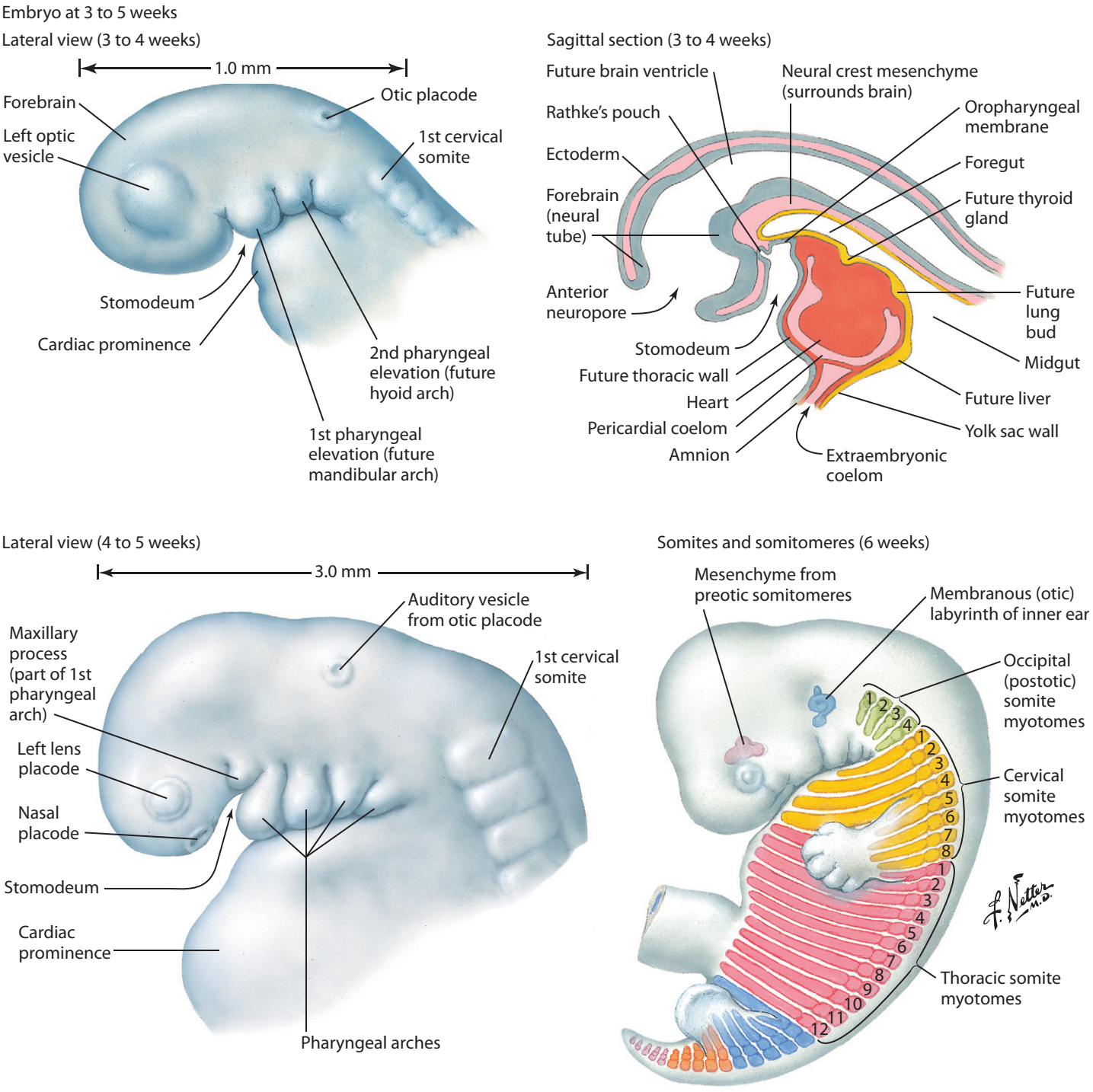
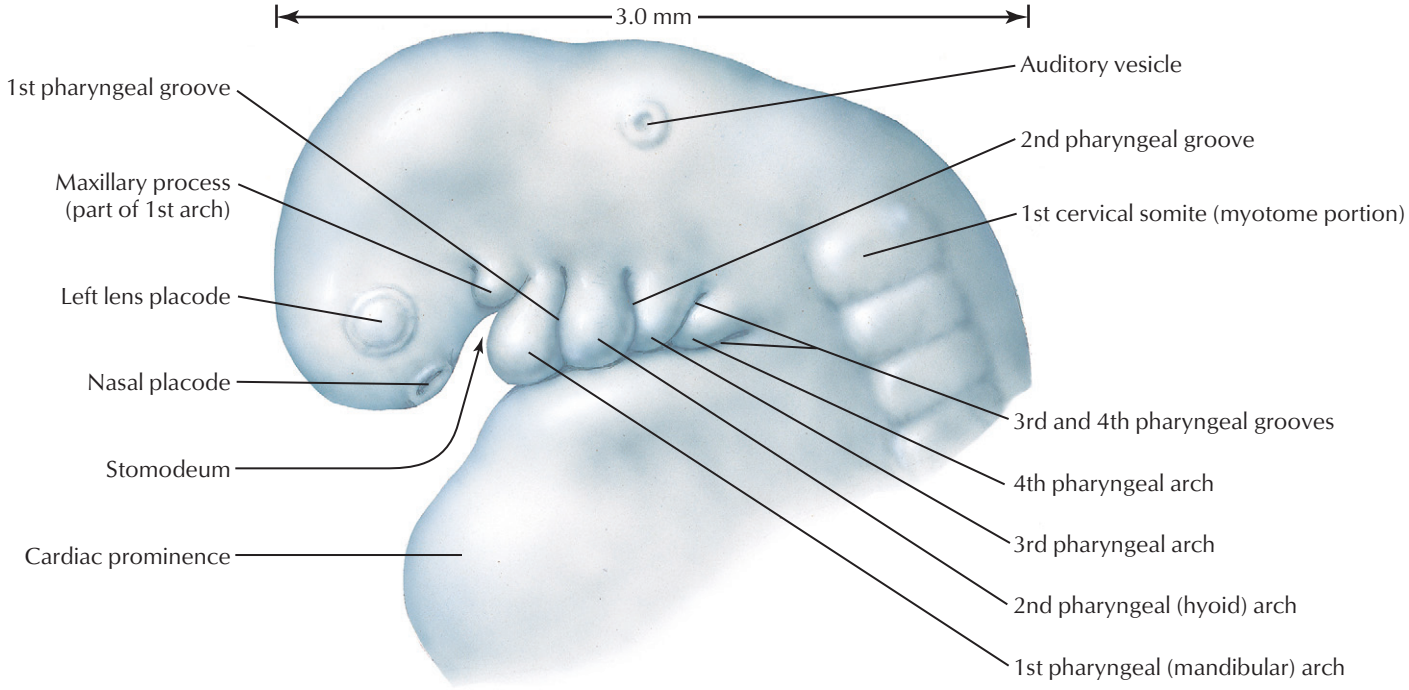


FIGURE 9.1 ECTODERM, ENDODERM, AND MESODERM

The surface ectoderm invaginates to form the **stomodeum,** the lining of the future oral cavity. The ectoderm thickens in three locations to form olfactory, lens, and otic **placodes** that relate to the special sensory cranial nerves I, II, and VIII, respectively. The endoderm of the foregut extends to the stomodeum and will line the pharynx, larynx, trachea, esophagus, and related structures.

Mesoderm in the head is in the form of **somites** and **head mesenchyme** from the **neural crest.** The latter surrounds the developing brain and forms the **pharyngeal arches** innervated by nerves V, VII, IX, and X. Postotic somites become tongue muscles (nerve XII), and preotic somitomeres form eye muscles (nerves III, IV, and VI).

Embryo at 4 to 5 weeks
Lateral view



Pharyngeal pouches and aortic arch arteries
Lateral view

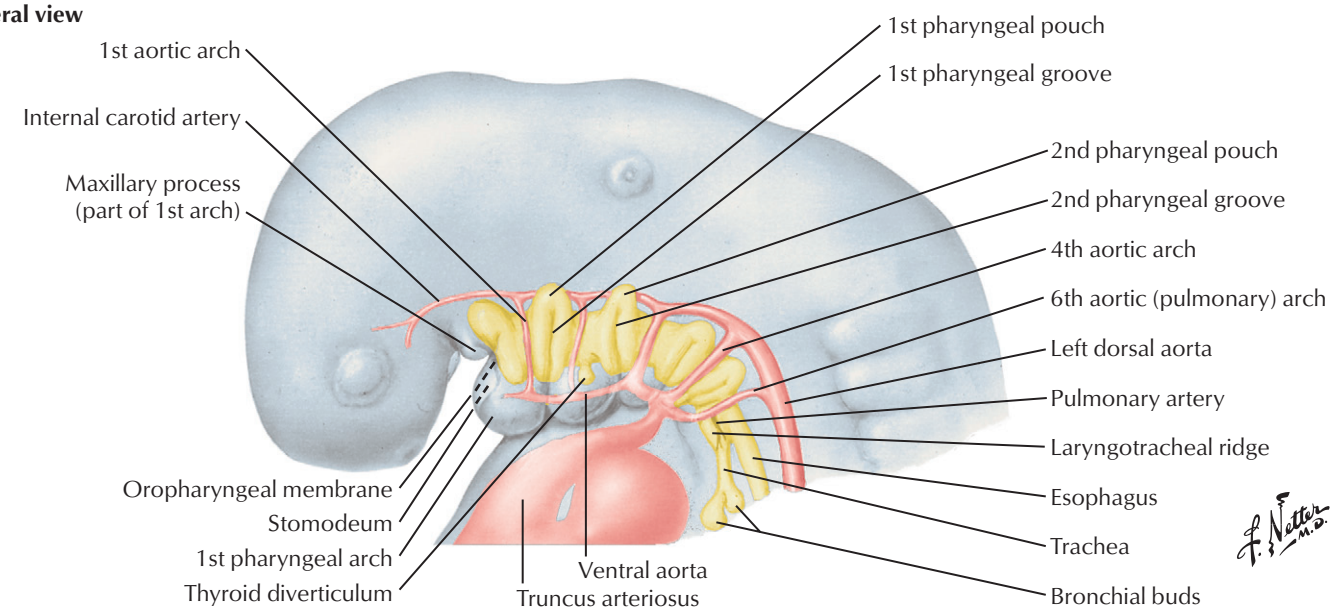


FIGURE 9.2 PHARYNGEAL (BRANCHIAL) ARCHES

The pharyngeal (branchial) arches are transverse swellings of mesenchyme that flank the foregut. They are covered with surface ectoderm on the outside and endoderm of the foregut on the inside. **Pharyngeal grooves** of ectoderm separate each pharyngeal arch on the surface, and **pharyngeal pouches** of foregut endoderm are their equivalent on the inside. Six arches originally evolved in fish as the primordia of the gill apparatus and viscerocranium. There are five arches in mammals, designated 1, 2, 3, 4, and 6 (arch 5 does not develop); they form most of the structures in the face and neck. Each mesodermal arch has a cranial nerve, a piece of cartilage, and an aortic arch artery.

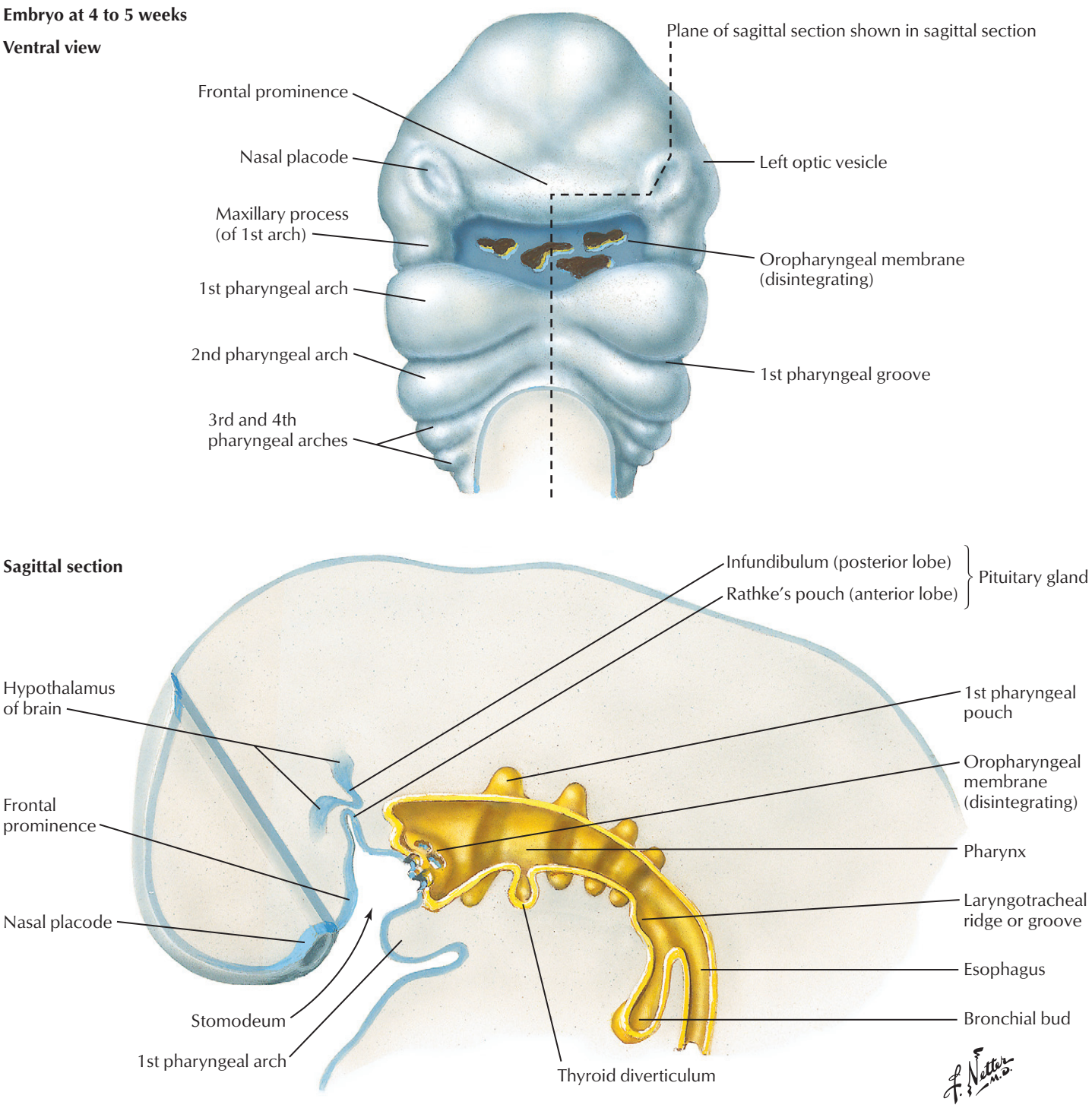


FIGURE 9.3 VENTRAL AND MIDSAGITTAL VIEWS

The first pharyngeal arch has maxillary and mandibular parts that form the lateral and inferior boundaries of the stomodeum, respectively. The maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve supply the two primordia. Because of its relationship to the stomodeum, the first pharyngeal arch has ectoderm on both the outside and inside, with more intense general sensory (somatic) innervation than the visceral sensory nerves that supply the endoderm on the inside of the other arches and the gut in general. The maxillary part of the first arch gives rise to the maxilla and structures of the midface with the exception of the nose. The mandibular arch develops into the mandible and related structures.

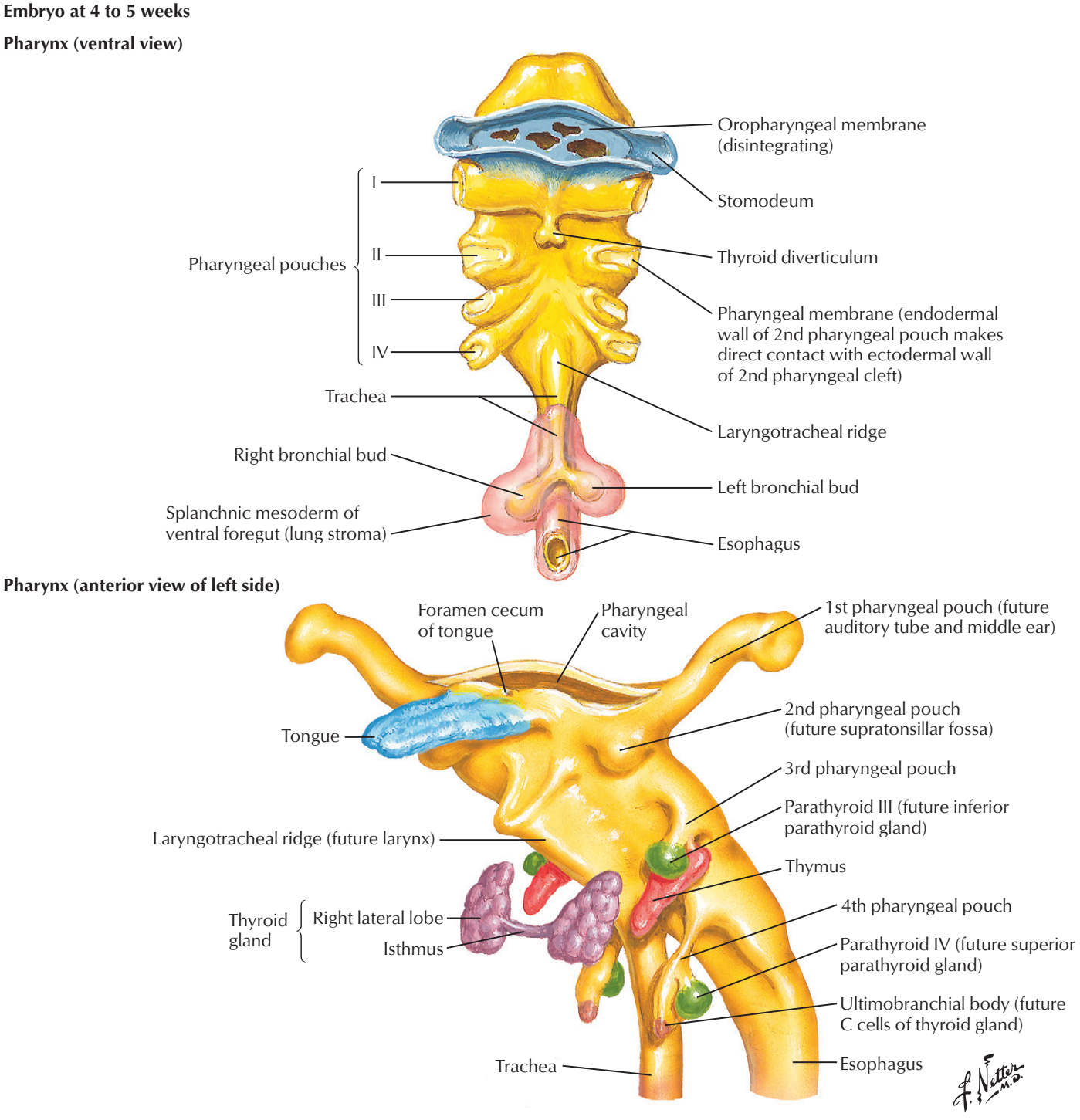


FIGURE 9.4 FATE OF THE PHARYNGEAL POUCHES

Pouch 1 forms the auditory tube, middle ear cavity, and mastoid air cells. Pouch 2 forms the epithelial crypts of the palatine tonsil. Epithelial cells from the rest of the pouches migrate to form the thymus gland (pouch 3), parathyroid glands (pouches 3 and 4), and parafollicular cells (C cells) of the thyroid gland (pouch 4). Parathyroid glands from pouch 3 become the inferior parathyroid glands as they descend with the thymus gland to a lower position than the superior parathyroid glands from pouch 4. The thyroid gland has its own diverticulum off the back of the tongue. It descends as a thyroglossal duct to its position anterior to the trachea.

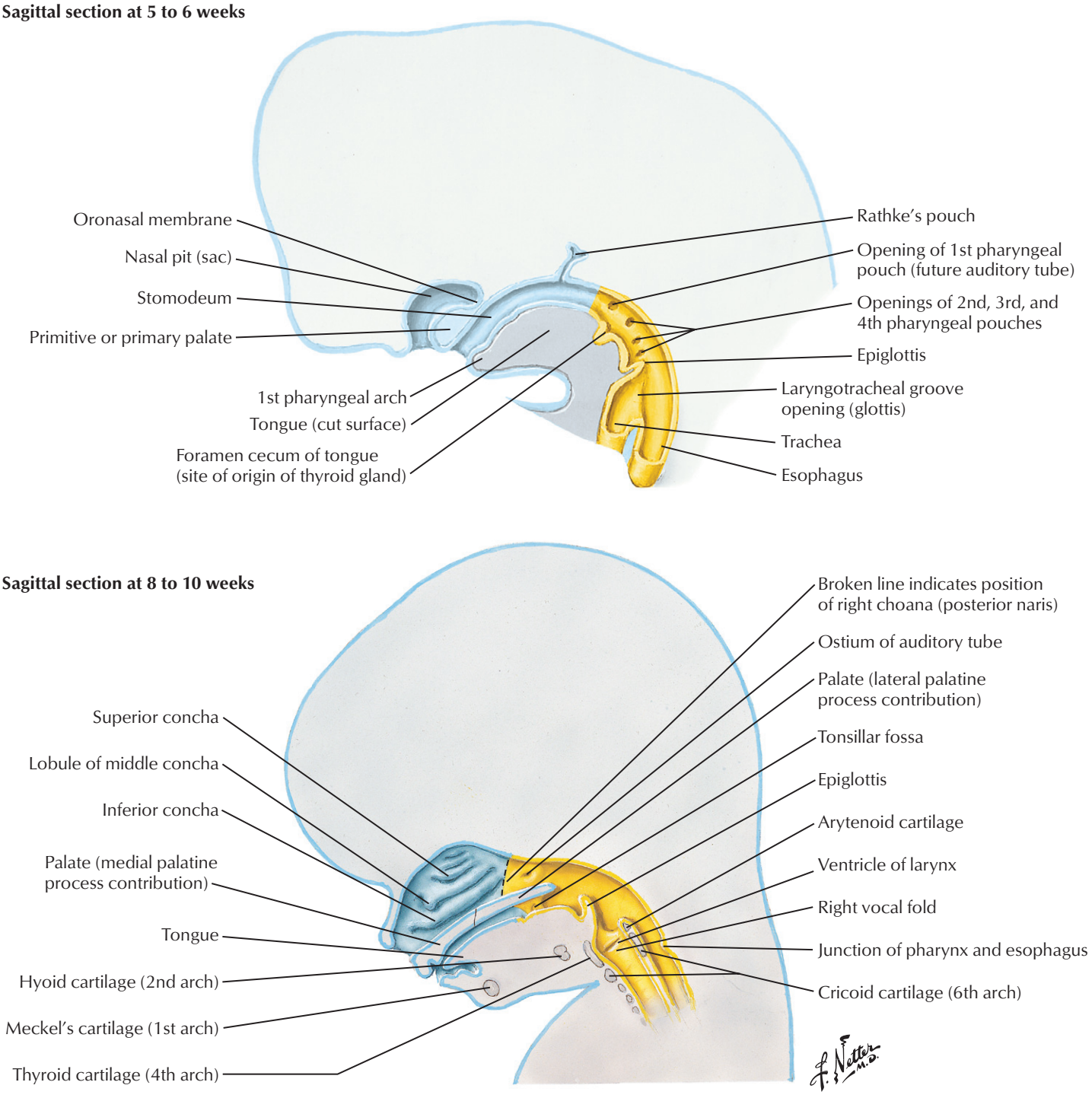
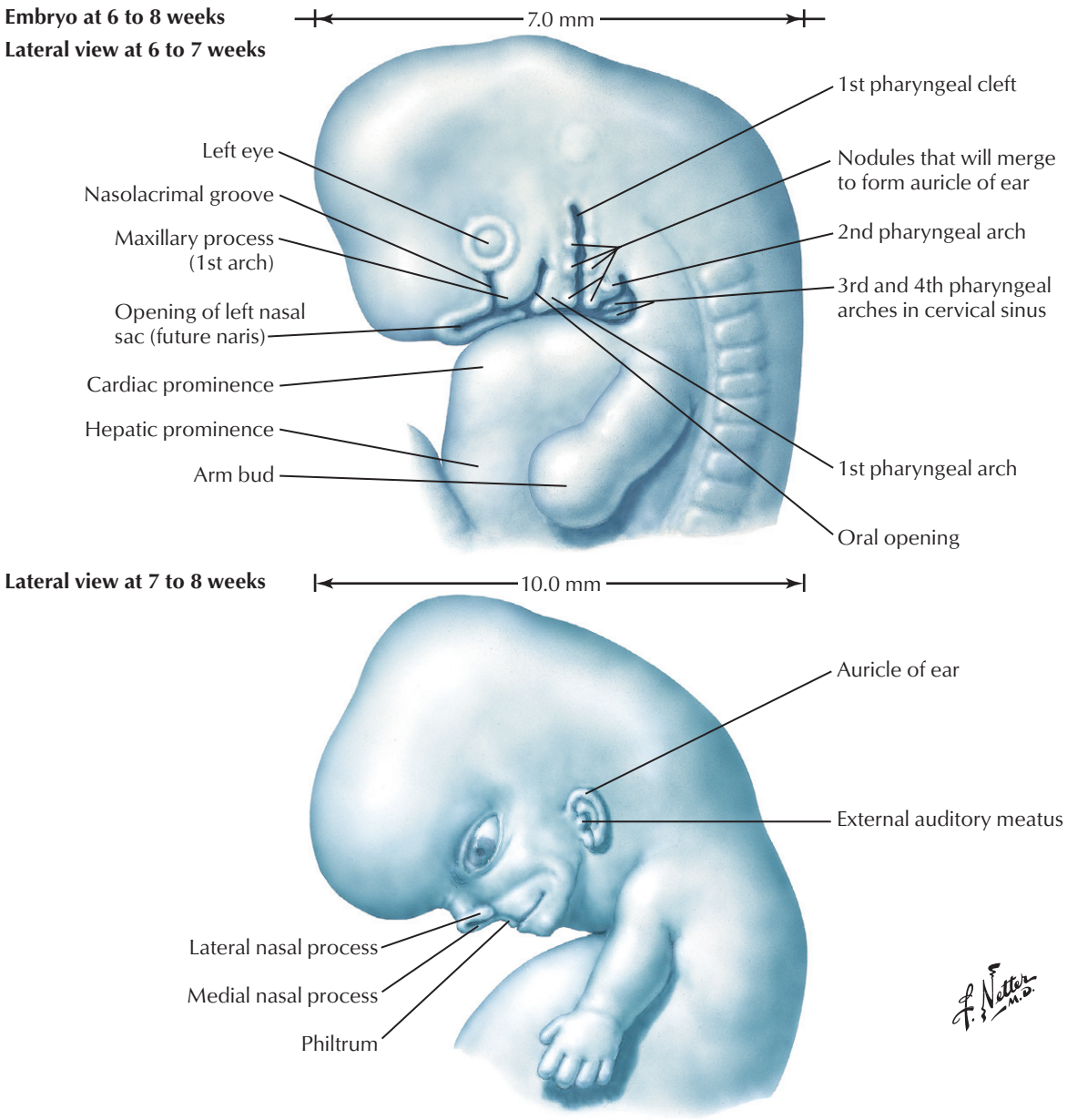


FIGURE 9.5 MIDSAGITTAL VIEW OF THE PHARYNX

Only the first and second pharyngeal pouches have derivatives visible in the pharynx after 10 weeks. The yellow in the bottom figure (8 to 10 weeks) shows the superior extent of the foregut where it joins the ectoderm of the nasal and oral cavities at the site of the former oropharyngeal membrane. The opening of the **auditory tube** (pouch 1) is clearly seen above the soft palate in the **nasopharynx.** Below the soft palate is the **oropharynx** with the **palatine tonsils** and their epithelial crypts derived from the second pharyngeal pouch. The laryngopharynx surrounds the epiglottis and entrance to the larynx. Epithelial cells from pouches 3 and 4 migrate to form glands, and the lateral walls of the pharynx behind and below the palatine tonsils are smooth.



PHARYNGEAL POUCH AND GROOVE DERIVATIVES

No.	From Pouches	From Grooves
1	Auditory tube, middle ear cavity, mastoid air cells	External auditory meatus
2	Palatine tonsil crypts	Cervical sinus (disappears)
3	Inferior parathyroids, thymus	Cervical sinus (disappears)
4	Superior parathyroids, parafollicular cells (C cells) of thyroid	Cervical sinus (disappears)

FIGURE 9.6 FATE OF THE PHARYNGEAL GROOVES

The ectoderm overlying arches 2 through 6 does not grow much and contributes little to the skin in the adult. Pharyngeal grooves 2, 3, and 4 merge together to form a **cervical sinus** that sinks below the surface and disappears. The external auditory meatus, the remnant of the first pharyngeal groove, is the only invagination on the side of the adult head and the only derivative of the pharyngeal grooves.

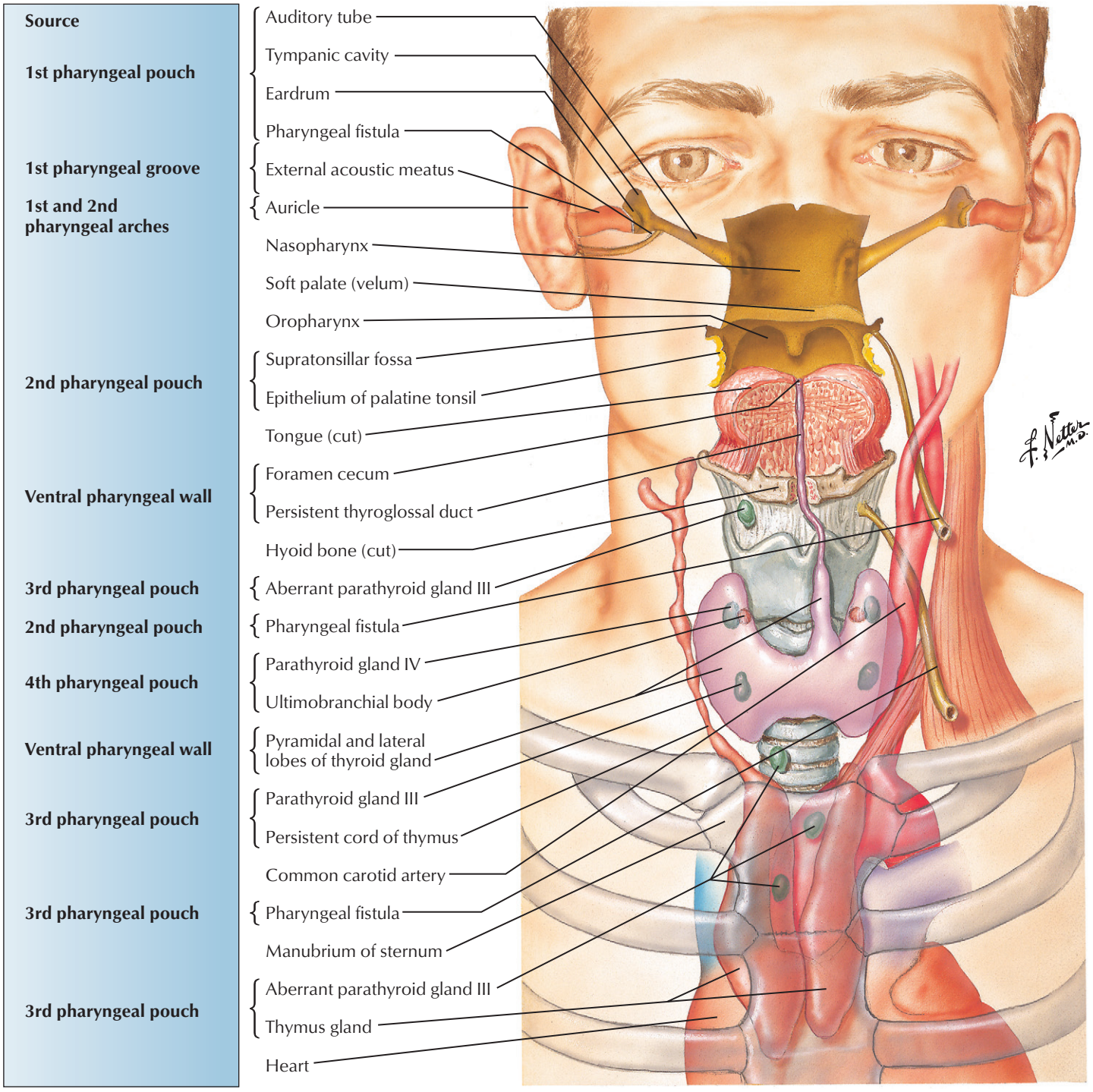


FIGURE 9.7 PHARYNGEAL GROOVE AND POUCH ANOMALIES

Most abnormalities of the pharyngeal apparatus are fistulas, sinuses, cysts, or ectopic glands or glandular tissue. There is a thin membrane of ectoderm and endoderm between each pharyngeal arch where a branchial groove abuts a pharyngeal pouch. If it breaks down, there is a communication between the surface and the pharynx lumen. It can persist as a fistula, sinus, or cyst, depending on the degree of continuity. The parathyroid and thymus glands can be undescended, or the latter can trail thymic tissue from the neck to the mediastinum. The thyroid gland can trail tissue along its path of descent or be entirely ectopic in the tongue, mediastinum, or anywhere in between. The thyroglossal duct can persist as cysts.

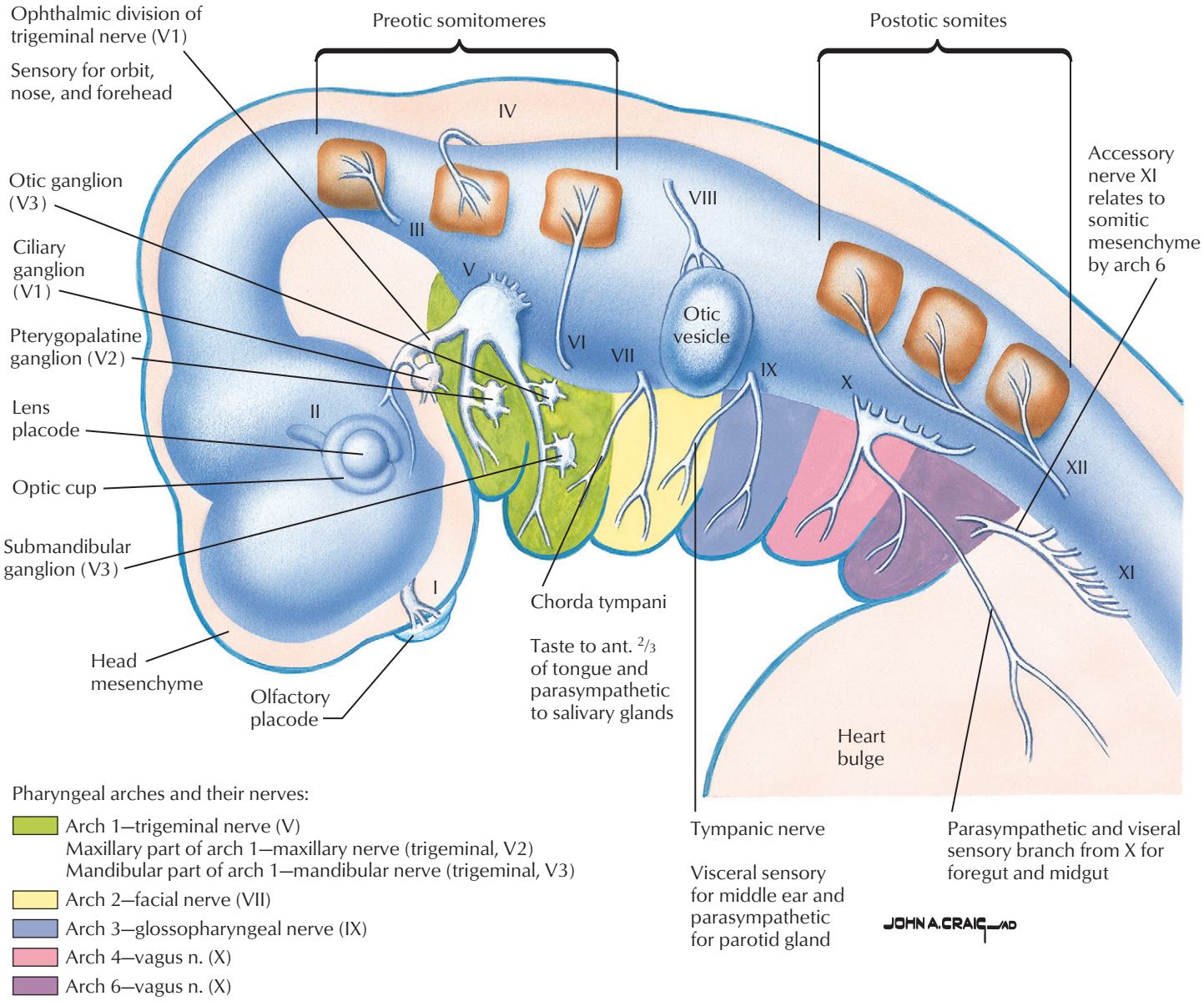


FIGURE 9.8 PHARYNGEAL ARCH NERVES

The pharyngeal arch nerves of the head and neck are mixed motor and sensory nerves. They are the segmental, territorial equivalents of the spinal nerve innervation of the rest of the body. The other cranial nerves are somatomotor or special sensory nerves for specific structures or functions. The cranial nerve for a typical arch contains motor neurons for skeletal muscles derived from the arches (called branchiomotor neurons), general sensory neurons for the ectodermal outside lining of the arch, and visceral sensory neurons for the inside lining of foregut endoderm.

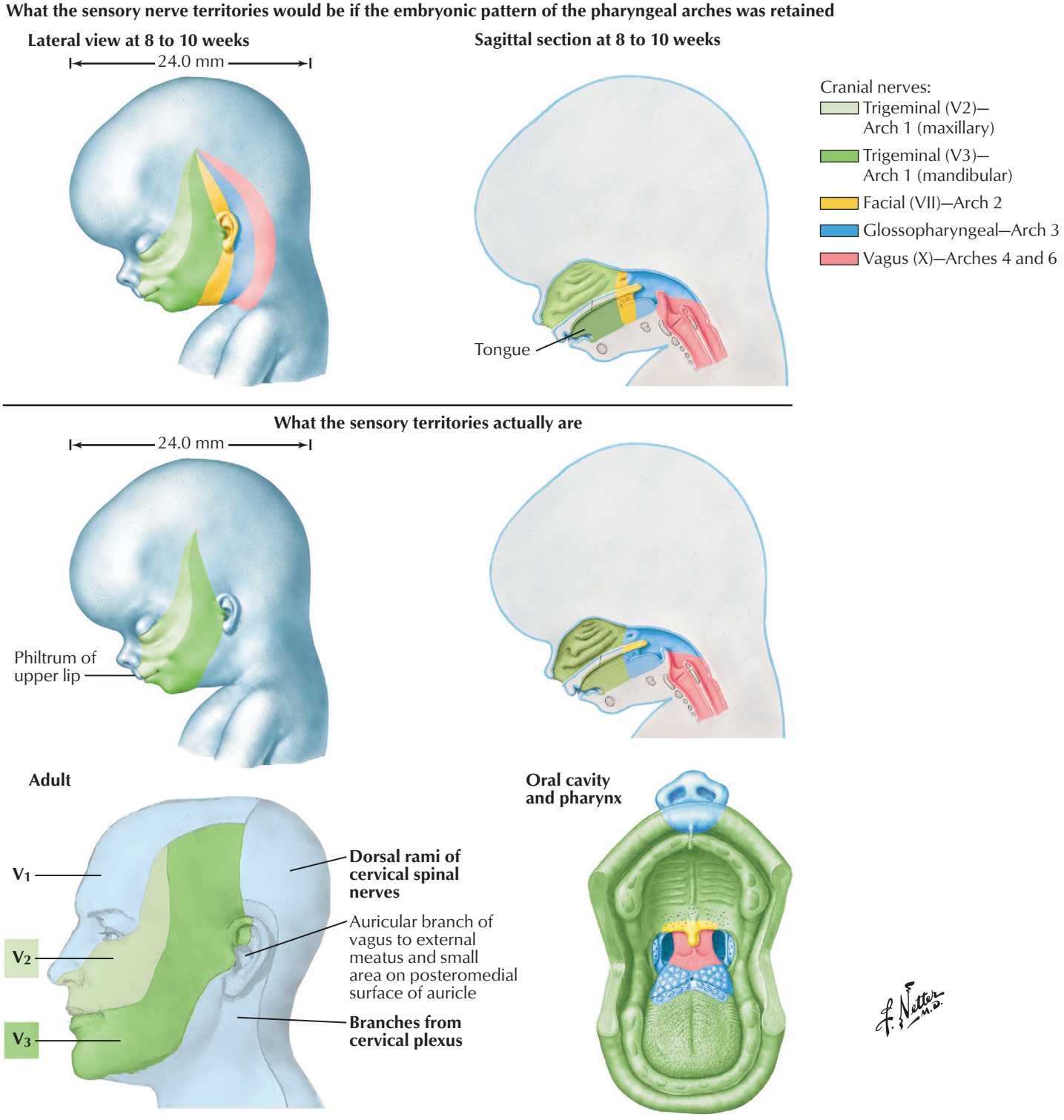


FIGURE 9.9 SENSORY INNERVATION TERRITORIES

The adult segmental pattern of cranial nerve innervation differs from the embryonic pattern because of two events:

1. The ectodermal linings on the surface of arches 2 through 6 do not grow. They merge into the cervical sinus and disappear. The result is that cervical spinal nerve territory is immediately below trigeminal nerve territory of the first pharyngeal arch.
2. The inside lining of arch 2 mostly disappears except, perhaps, for a little sensation on the soft palate. The back of the tongue behind arch 1 territory should be innervated by the facial nerve, but it is supplied by the glossopharyngeal nerve from arch 3.

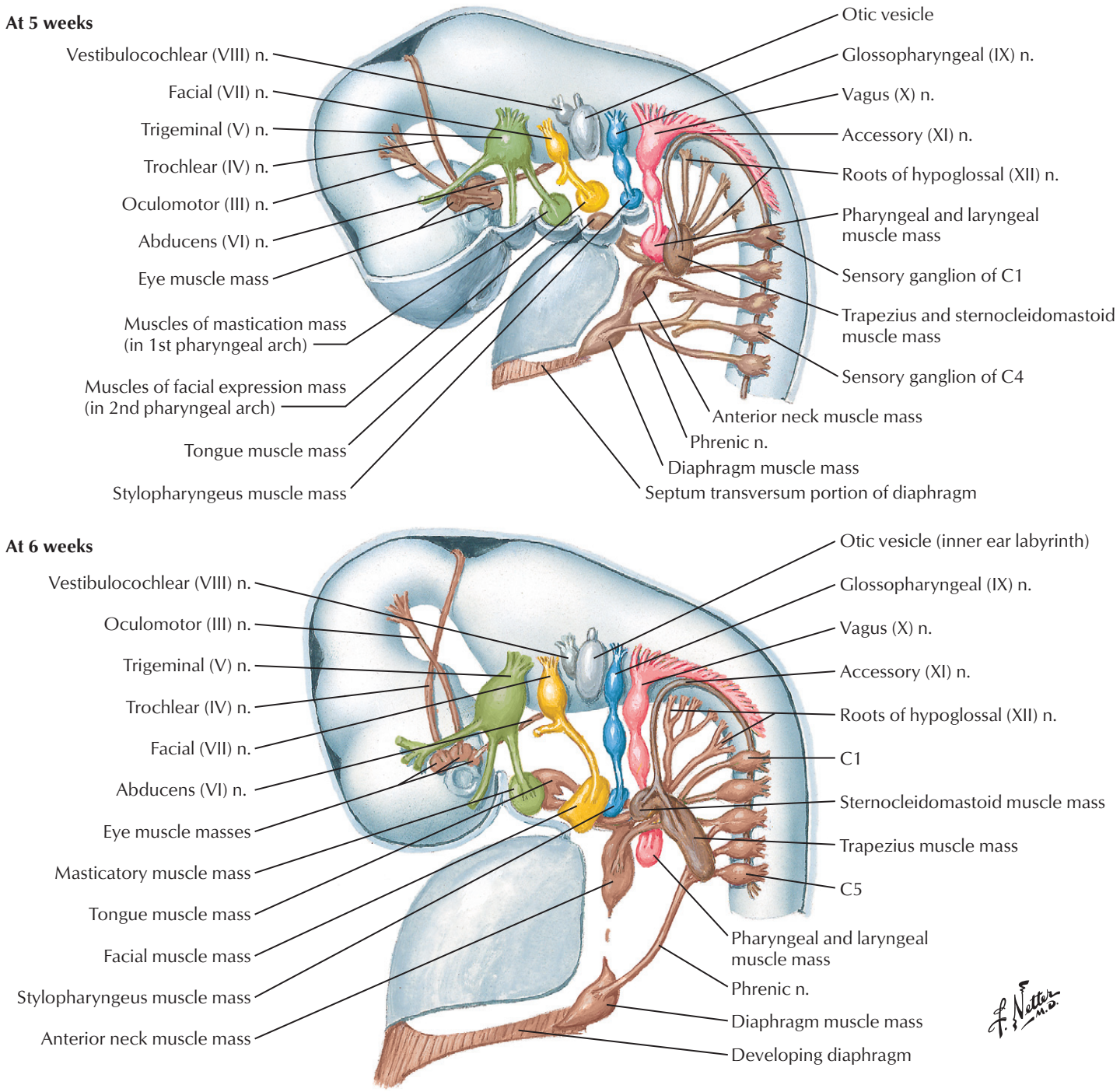


FIGURE 9.10 EARLY DEVELOPMENT OF PHARYNGEAL ARCH MUSCLES

The neural crest mesenchyme in the pharyngeal arches gives rise to the connective tissue component of muscles (tendons, epimysium, perimysium, and endomysium). Cells from somite myotomes migrate into the arches to differentiate into muscle cells. The pattern is the same as for muscle development in the limb buds: The muscle cells are somitic in origin, and the connective tissue comes from local mesenchyme (somatopleure in the limbs and neural crest in the pharyngeal arches). The first arch gives rise to the muscles of mastication, the second arch to the muscles of facial expression, the third to the stylopharyngeus muscle, and the fourth to the laryngeal muscles and constrictors of the pharynx.

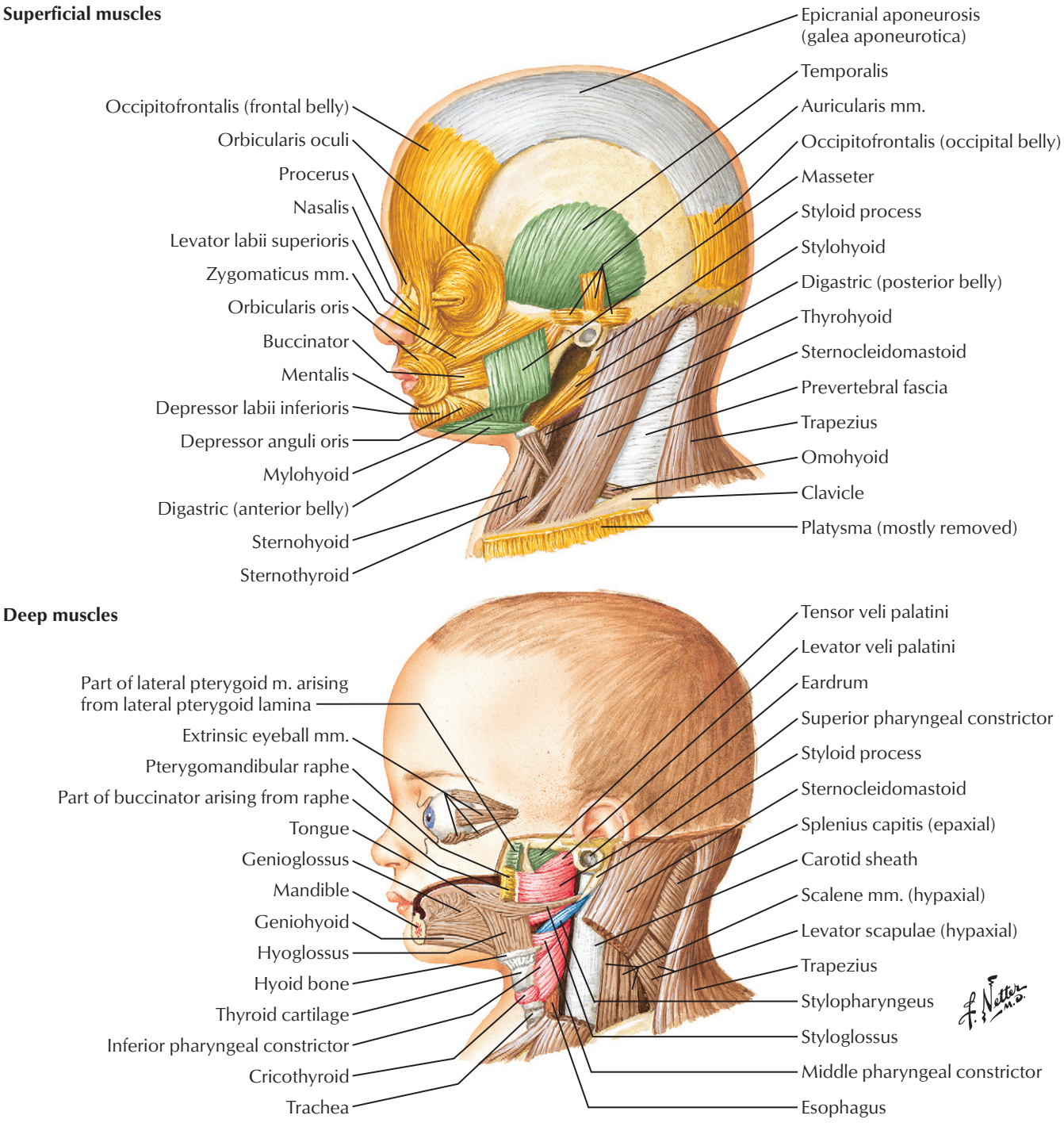
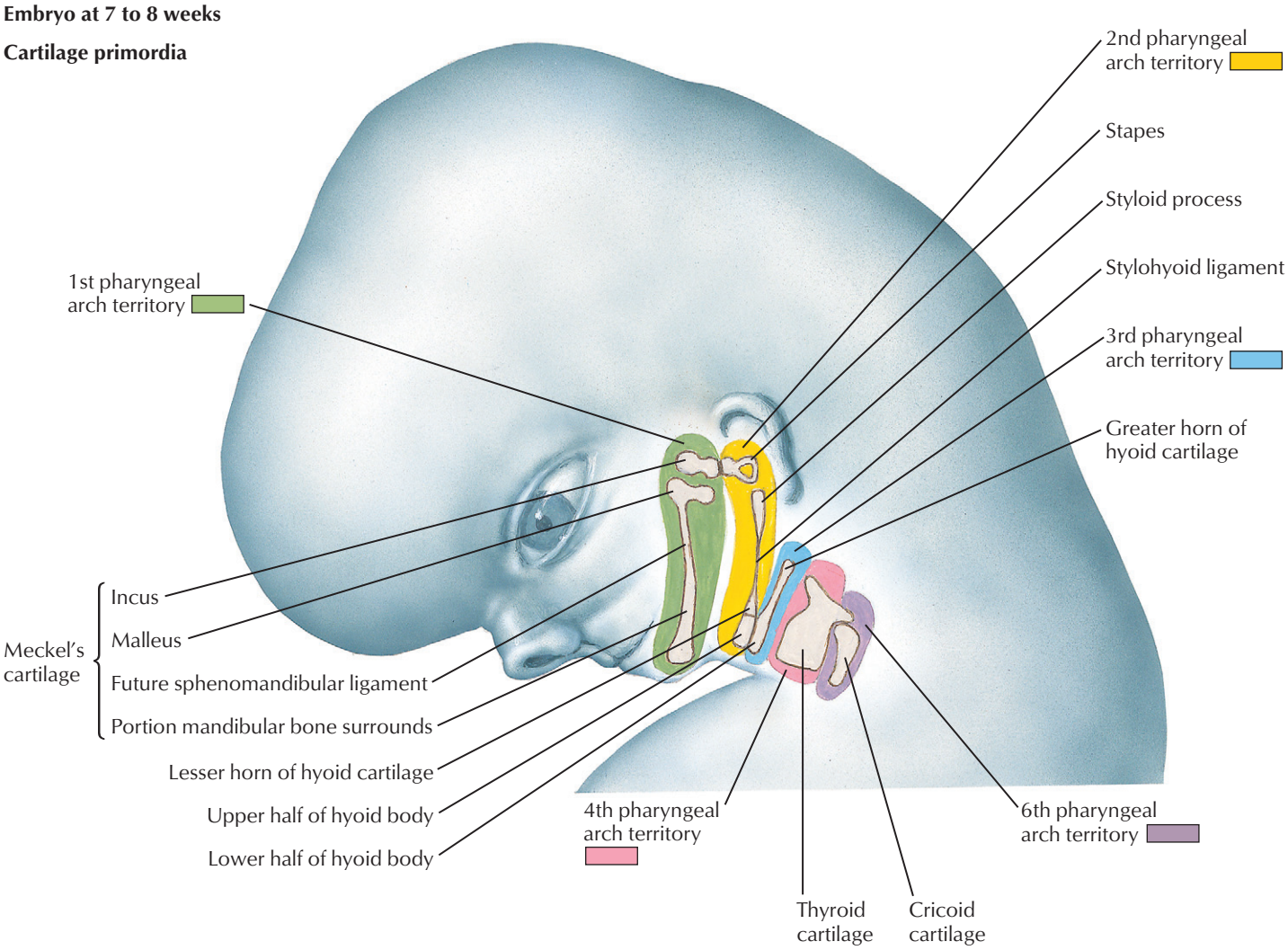


FIGURE 9.11 LATER DEVELOPMENT OF PHARYNGEAL ARCH MUSCLES

The extraocular eye muscles originate from preotic somitomeres and are supplied by cranial nerves III (oculomotor), IV (trochlear), and VI (abducens). The tongue muscles develop from postotic somites innervated by the hypoglossal nerve (XII). Somitic muscles innervated by cervical spinal nerves are the infrahyoid "strap" muscles of the neck and the diaphragm. The trapezius and sternocleidomastoid muscles originate from an early migration of somitic cells in the vicinity of the sixth pharyngeal arch. They are innervated by the accessory nerve, a "cranial" nerve (XI) that arises from the cervical spinal cord. The former spinal root of the accessory nerve is now the accessory nerve proper, and the former cranial root of XI is part of the vagus nerve.



PHARYNGEAL ARCH BONES AND CARTILAGE

Arch #	Derivatives of Arch Cartilages
1	Malleus, incus, sphenomandibular ligament
2	Stapes, styloid process, stylohyoid ligament, upper half of hyoid
3	Lower half and greater horns of hyoid
4	Thyroid and epiglottic cartilages of larynx
6	Cricoid, arytenoid, and corniculate cartilages of larynx

FIGURE 9.12 PHARYNGEAL ARCH CARTILAGES

The mandible primarily develops from intramembranous ossification of first branchial arch mesenchyme that condenses around Meckel's cartilage. Secondary cartilages appear in arch 1 mesenchyme to form endochondral bone of the mandibular condyle, symphysis, and coronoid process.

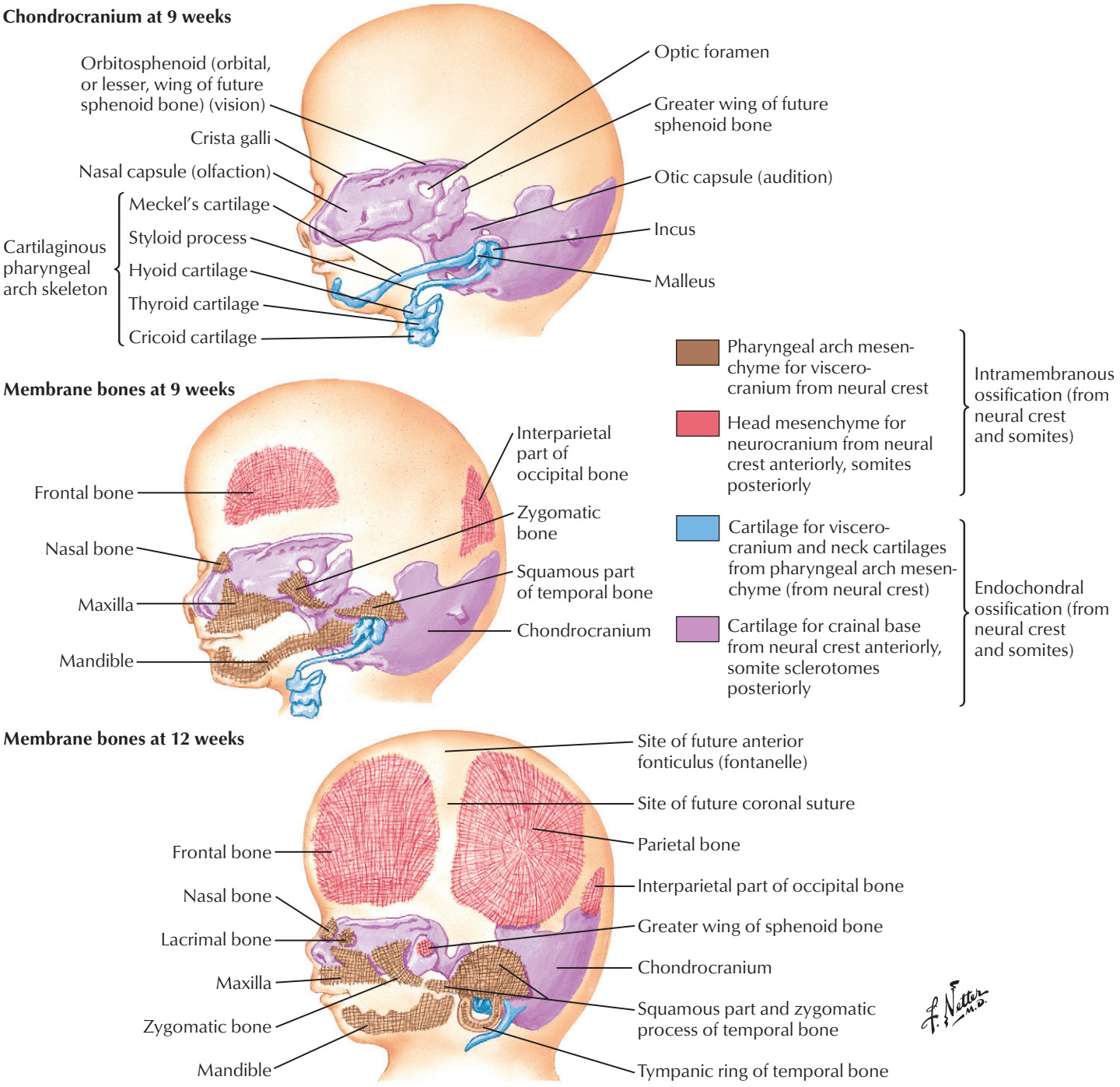


FIGURE 9.13 OSSIFICATION OF THE SKULL

The skull develops from both intramembranous and endochondral ossification, and the source of mesenchyme or cartilage depends on whether a bone is anterior or posterior in the skull regardless of the type of ossification. Bones anterior to the coronal suture and middle of the sphenoid bone develop from neural crest mesenchyme. Bones posterior to these boundaries develop from paraxial mesoderm (somites). The frontal bone develops via intramembranous ossification from mesenchyme from the neural crest. The parietal bones and the upper, interparietal part of the occipital bone are also from intramembranous ossification, but the

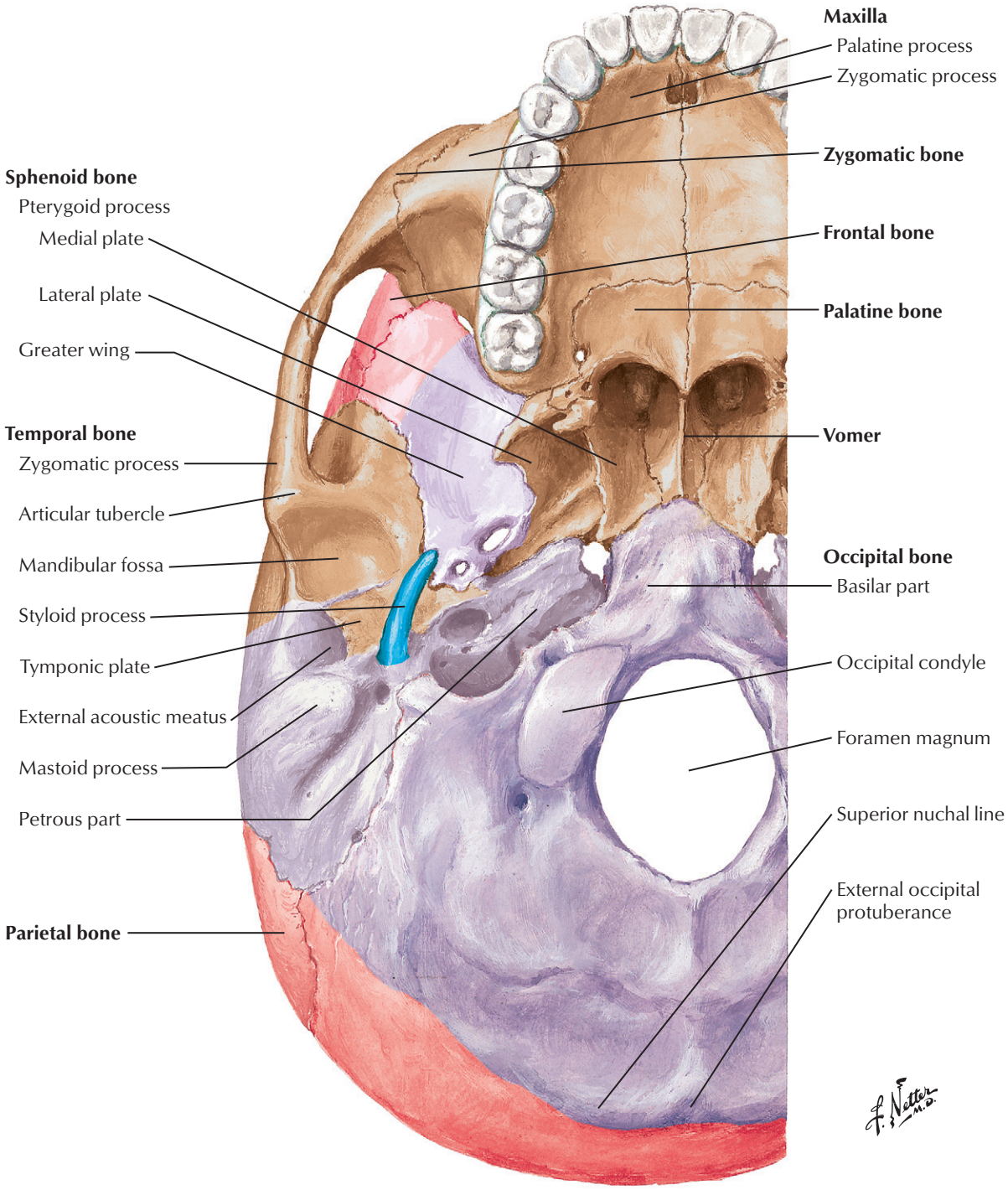


FIGURE 9.13 OSSIFICATION OF THE SKULL, CONTINUED

source of mesenchyme is paraxial mesoderm, not neural crest. Endochonral bone of the cranial base comes from neural crest mesenchyme anteriorly (ethmoid bone, anterior half of the sphenoid) and somite sclerotomes posteriorly (posterior half of the sphenoid, petrous and mastoid parts of the temporal bone, and basilar, condylar, and lower squamous part of the occipital bone).

All of the endochondral and intramembranous bones that develop from the pharyngeal (branchial) arches come from neural crest cells that invade the arches to form most of their mesenchyme. Some bones, such as the temporal and sphenoid bones, develop from both types of ossification.

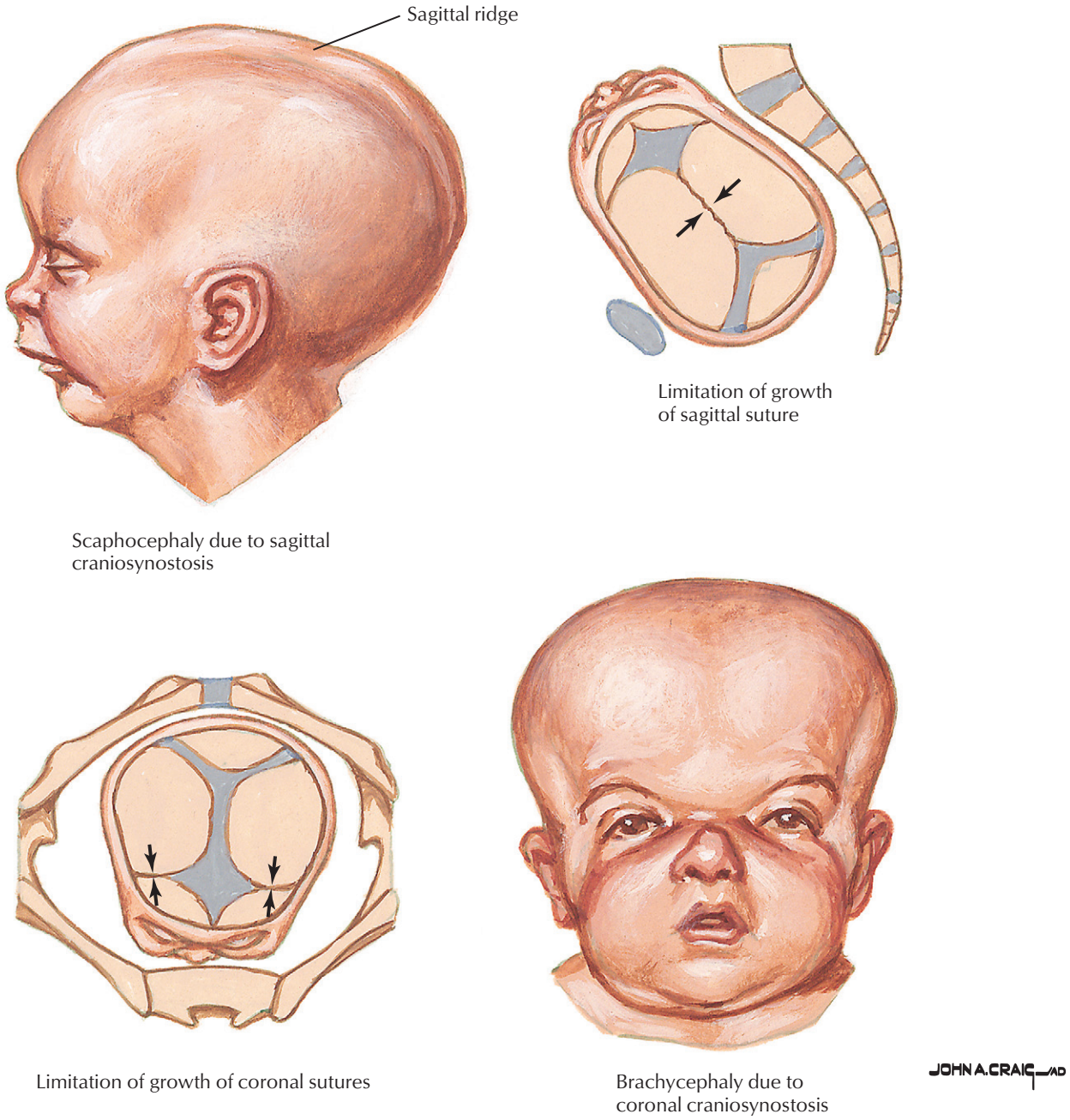
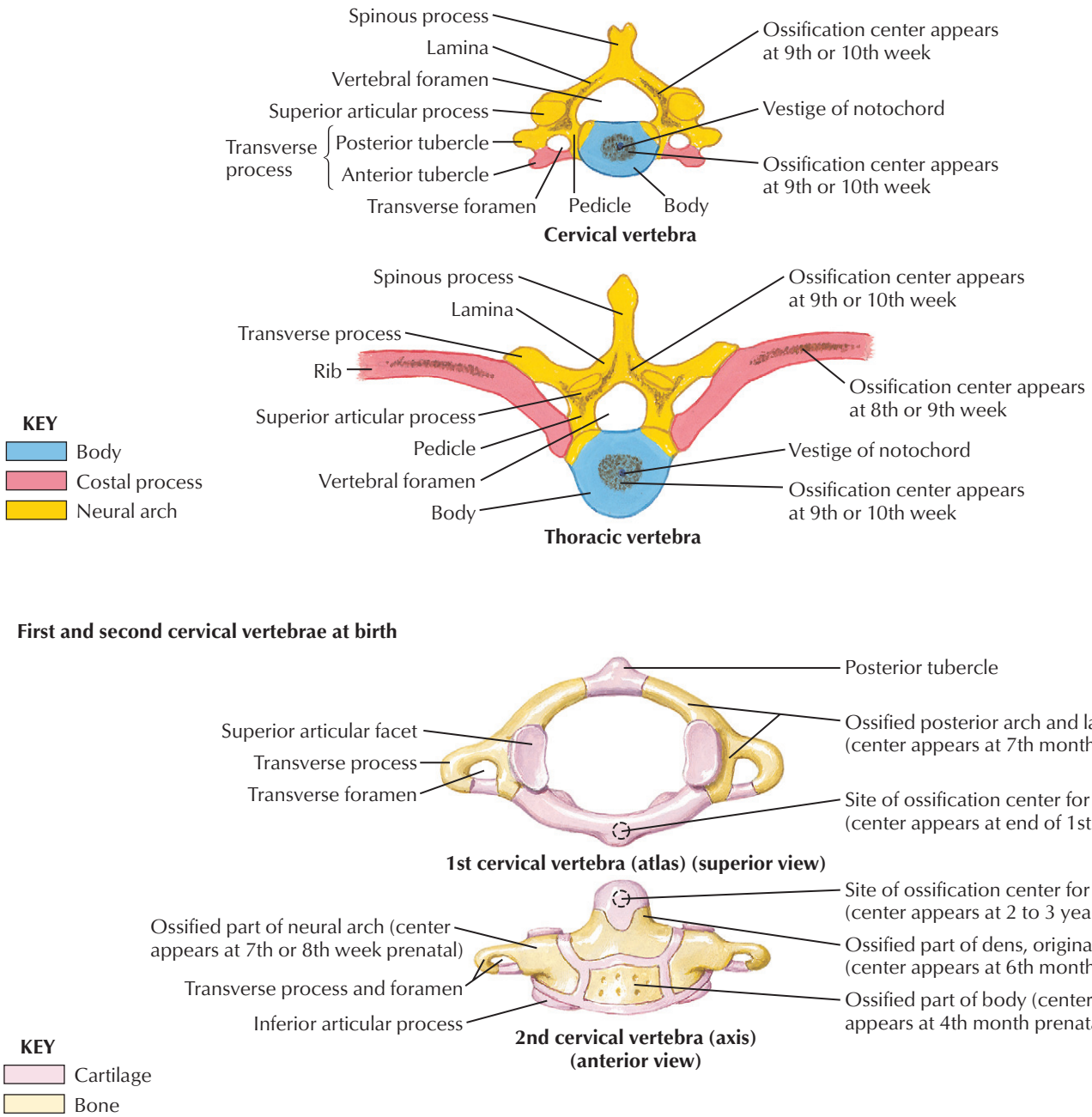


FIGURE 9.14 PREMATURE SUTURE CLOSURE

Enlargement of the neurocranium occurs by bony deposition at the sutures. If the process is interrupted at one suture, growth in the direction of deposition is impeded, and compensation occurs by more rapid deposition in the other sutures. Premature closure of the sagittal suture prevents growth in width and results in a long, narrow neurocranium. The viscerocranium is largely unaffected. Growth compensation for early closure of the coronal or lambdoidal suture produces a short, wide neurocranium. Premature closure can be caused by a difficult birth (shown above) or genetic factors and can involve only one side of the skull. Normal fusion begins in the 20s at the top of the skull and proceeds throughout life toward the ear region.

Fate of body, costal process, and neural arch components of cervical and thoracic vertebra, with sites and time of appearance of ossification centers



First and second cervical vertebrae at birth

FIGURE 9.15 CERVICAL OSSIFICATION

Cervical vertebrae develop from the endochondral ossification of somite sclerotome mesoderm that condenses around the neural tube. The anterior tubercle of the transverse process is homologous to the rib ossification center related to a thoracic vertebra. The body of the atlas (C1) fuses to the axis (C2) to form the odontoid process or dens. Most cervical ossification anomalies produce the fusion of adjacent vertebra. This can involve most of the cervical spine (Klippel-Feil Syndrome), C2 to C3, the atlas to the occipital bone, or the dens to the atlas (os odontoideum). Intervertebral joint instability between the atlas and axis can result, narrowing the vertebral canal upon flexion and extension with possible spinal cord damage.

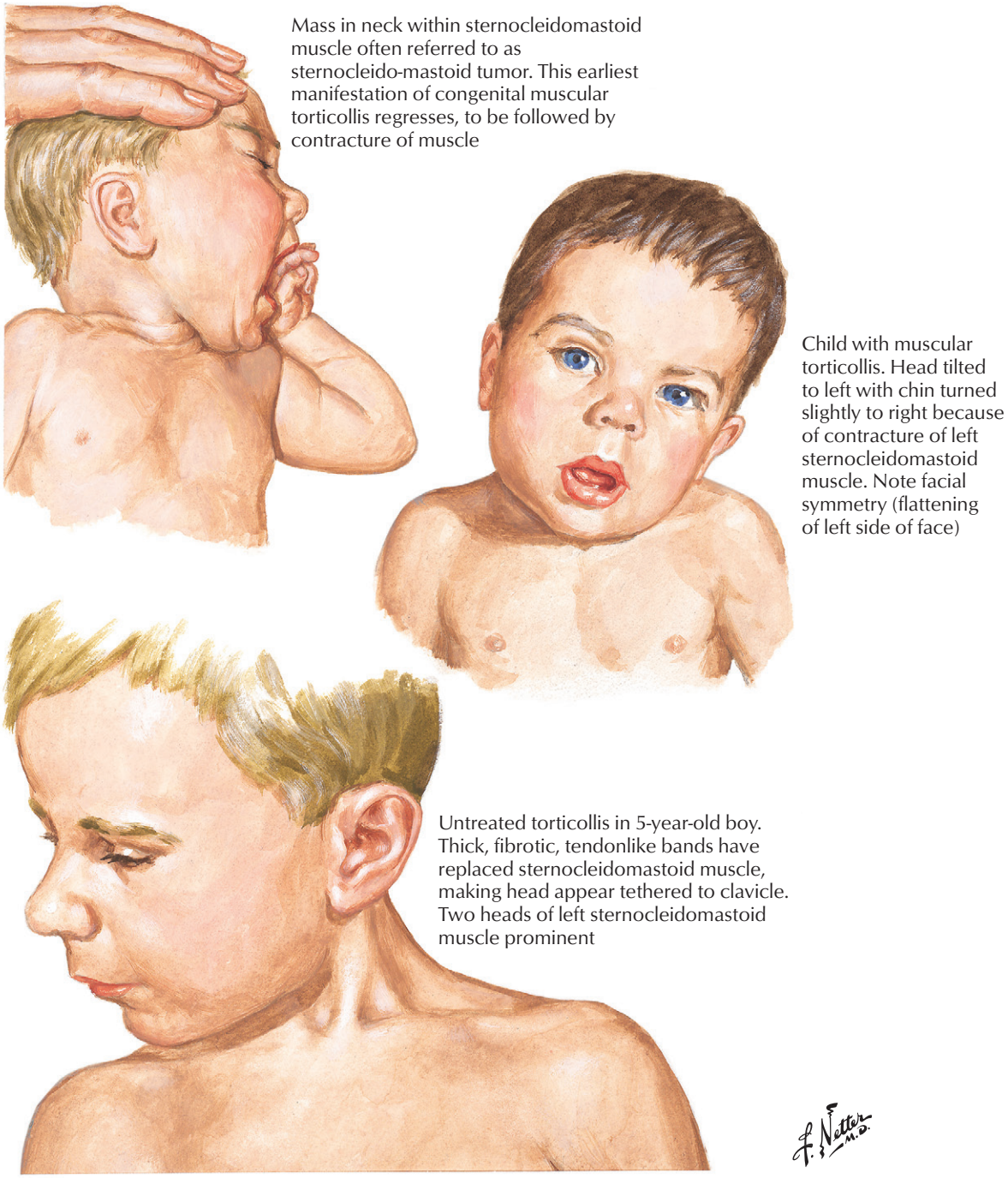


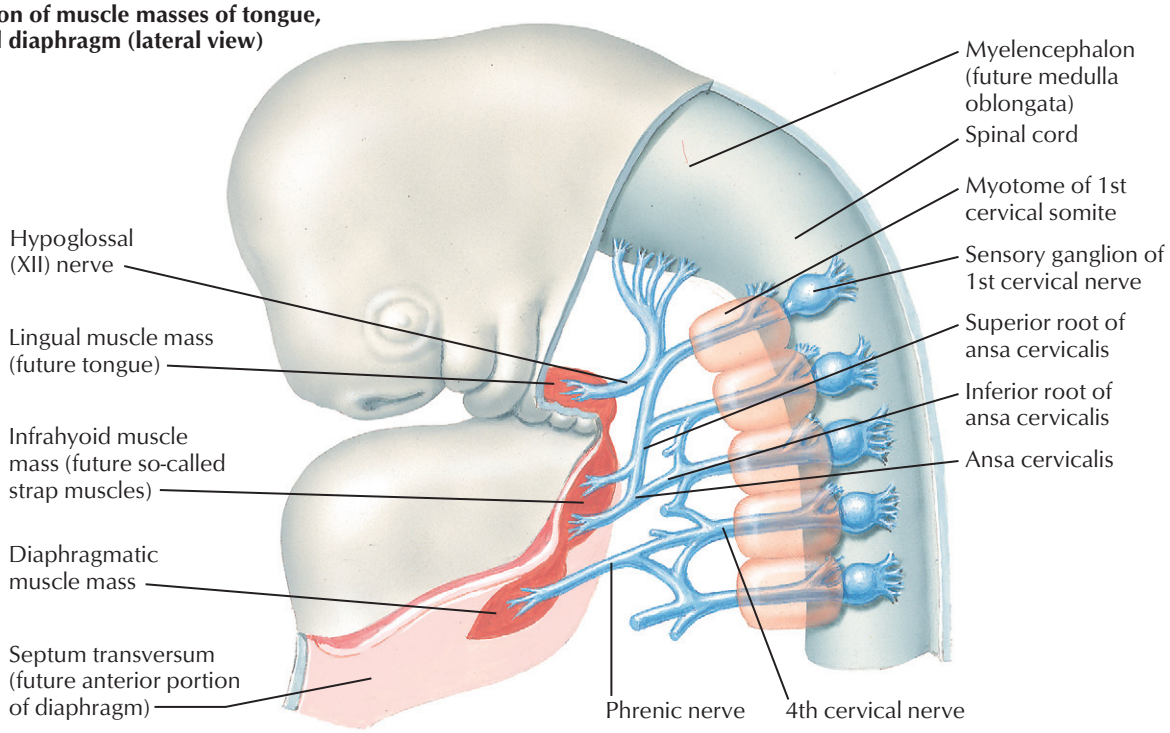
FIGURE 9.16 TORTICOLLIS

Torticollis literally means a twisting of the neck and can be caused by partial disarticulation (subluxation) and fixation of the atlas and axis, or more commonly by damage to or dysfunction of one sternocleidomastoid muscle. The result is a shortening or contracture of one sternocleidomastoid muscle that puts the head and neck in a configuration that is a sum of all the actions of the muscle on the affected side:

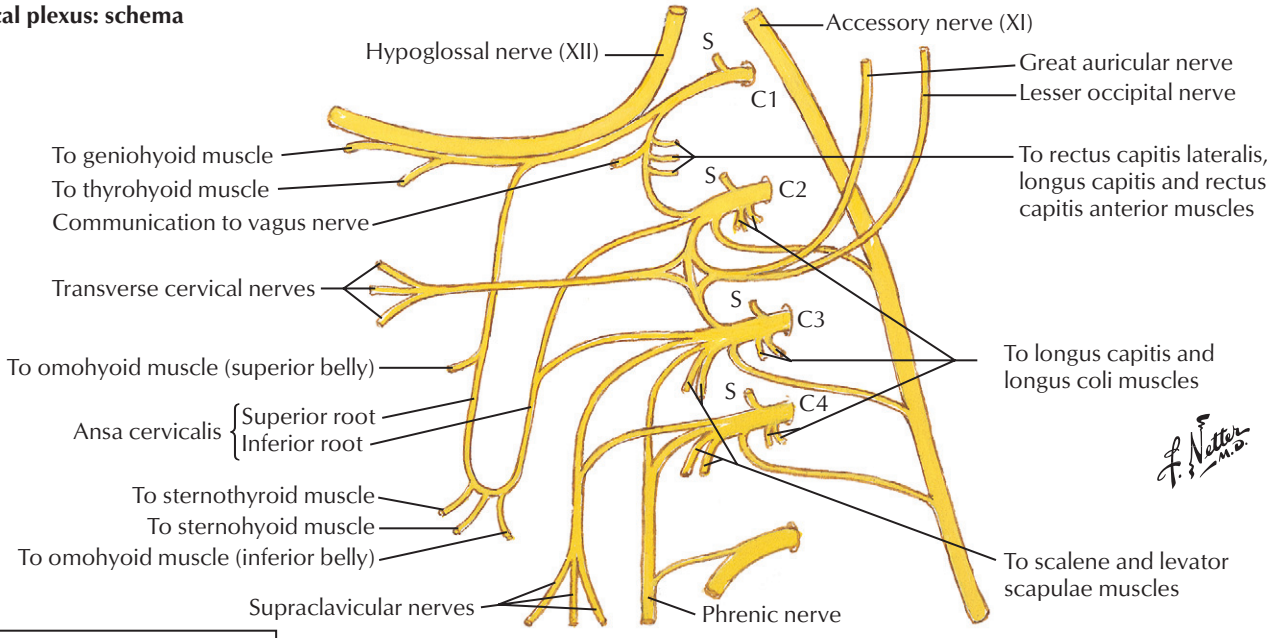
- Flexion of the neck at the lower cervical intervertebral joints
- Extension at the atlanto-occipital joint
- Lateral bending of the neck at cervical intervertebral joints
- Rotation of the head and neck (at all cervical intervertebral joints) to the opposite side of the contracting muscle

The cervical plexus and hypoglossal nerve in a 5- to 6-week embryo

Innervation of muscle masses of tongue, neck, and diaphragm (lateral view)



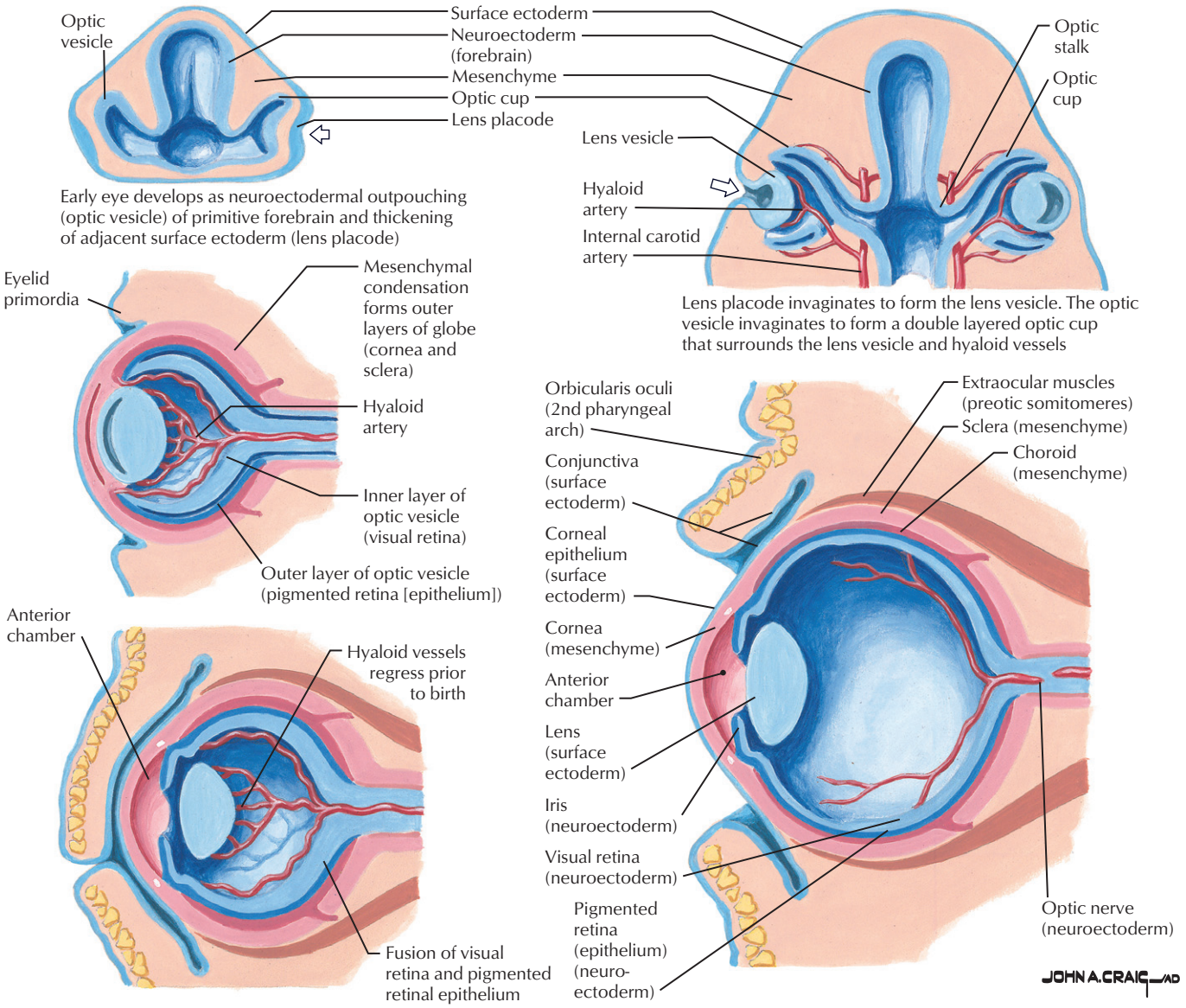
Cervical plexus: schema



Note:
S = Gray ramus from superior cervical sympathetic ganglion

FIGURE 9.17 CERVICAL PLEXUS

The cervical plexus of spinal nerves supplies the infrahyoid strap muscles, diaphragm, and other neck muscles. It is closely related to cranial nerve XII, the hypoglossal nerve. Both innervate muscles derived from sequential somites that continue from the neck into the head. This explains why some C1 fibers end up in the sheath of the hypoglossal nerve. The **ansa cervicalis,** the **phrenic nerve,** and direct branches to the scalene muscles, levator scapulae, and the longus capitis and colli muscles are the main motor components of the cervical plexus. Cutaneous branches are the greater auricular, lesser occipital, transverse cervical, and suprascapular nerves.



PRIMORDIA AND DERIVATIVES

Primordium	Derivative	Related Nerve
Optic cup	Retina, optic nerve, ciliary and iris epithelium, and pupil constrictor and dilator muscles	Optic nerve (II)
Head mesenchyme	Cornea, sclera, meninges, choroid, ciliary muscle and connective tissue, and iris connective tissue	Ophthalmic nerve (V1)
Somites	Extraocular eye muscles	III, IV, and VI
Surface ectoderm	Eyelid epidermis, conjunctiva, lacrimal gland	Ophthalmic nerve (V1)
2nd pharyngeal arch	Orbicularis oculi muscle	Facial nerve (VII)
Lens placode	Lens	

FIGURE 9.18 ORBIT

The retina and optic nerve develop as a double-layered extension of the neural tube that surrounds the lens vesicle of surface origin. The optic cup has a ventral cleft for blood vessels. The iris is at the reflection of the two layers, and both it and the ciliary body are formed in part from optic cup epithelium. The two layers of the optic cup never become firmly attached. This is the embryonic basis of detached retina and resulting blindness.

Connective tissue elements of the eye—sclera, cornea, and the vascular choroid layer—develop from a condensation of head mesenchyme around the optic cup. Extraocular muscles come from somitomeres. The epidermis of the eyelids develops from surface ectoderm and is continuous with the conjunctiva and corneal epithelium.

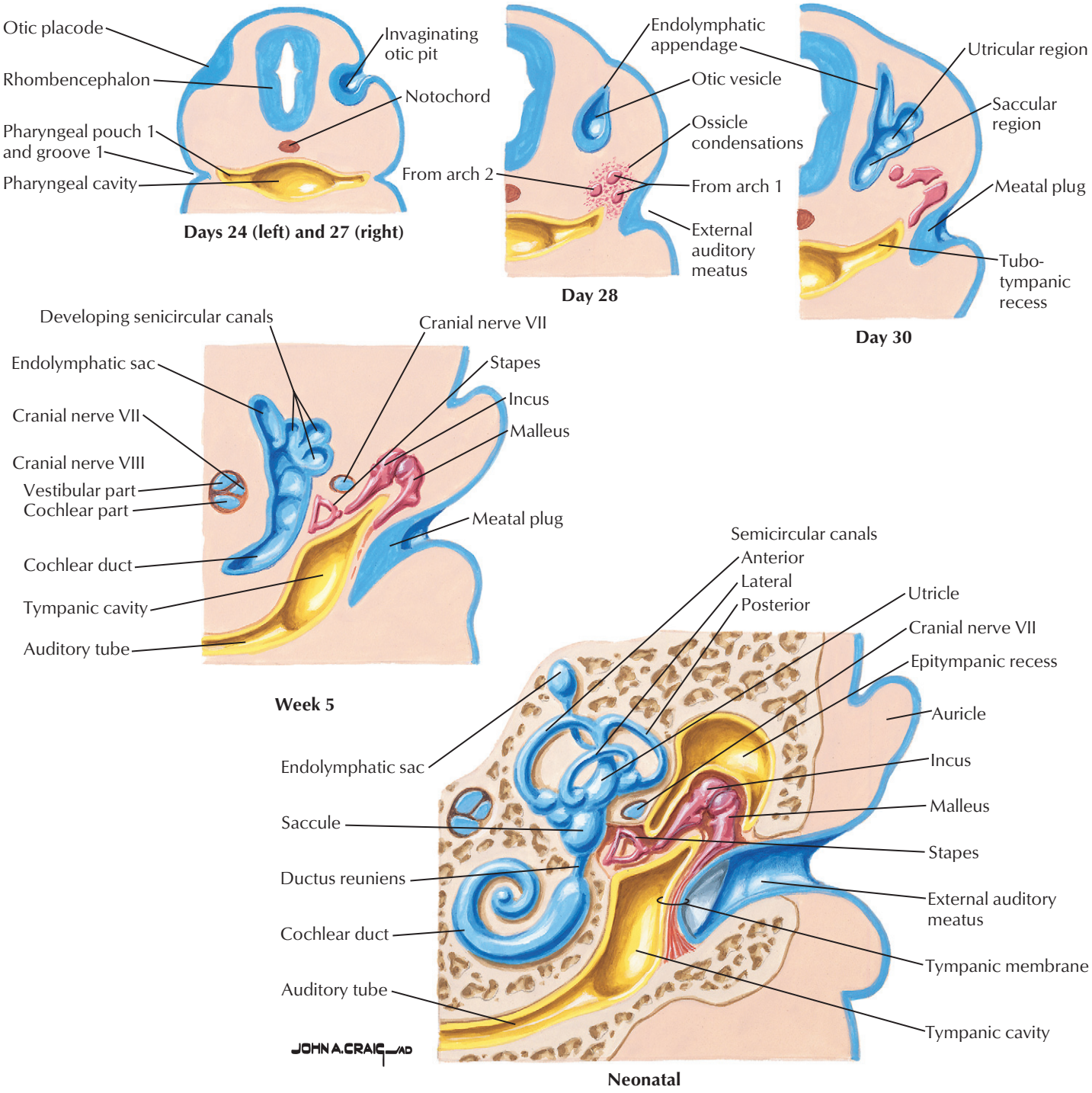
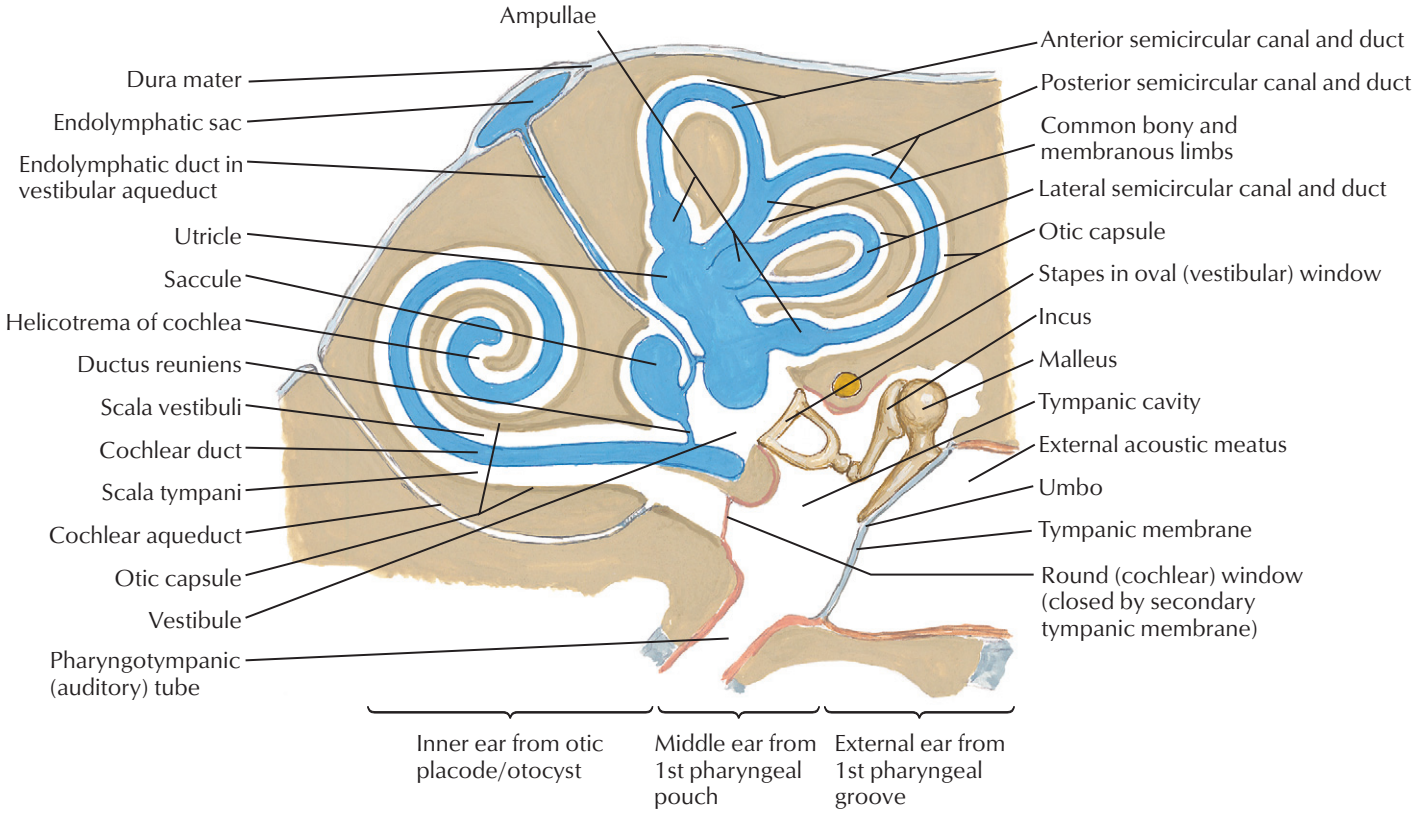


FIGURE 9.19 EAR DEVELOPMENT

The ear is organized into external, middle, and inner parts that differ from each other in structure and embryonic origins. The external ear consists of the auricle and external auditory meatus extending to the tympanic membrane (eardrum). The middle ear cavity, an extension of the nasopharynx housing the three ear ossicles, is deep to the tympanic membrane. The external auditory meatus and middle ear develop from the first pharyngeal groove and pouch, respectively. The otic placode gives rise to the inner ear, which consists of the organs of hearing and balance: the cochlea and vestibular apparatus (saccule, utricle, and semicircular canals). These are imbedded in the petrous part of the temporal bone.

Bony and membranous labyrinths: schema



Section through turn of cochlea

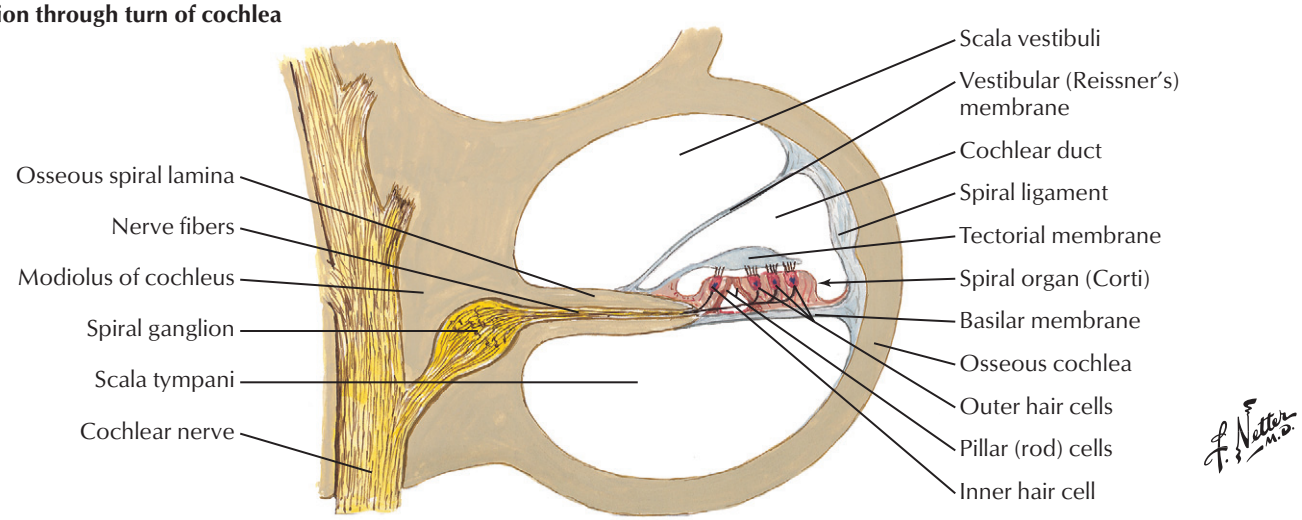
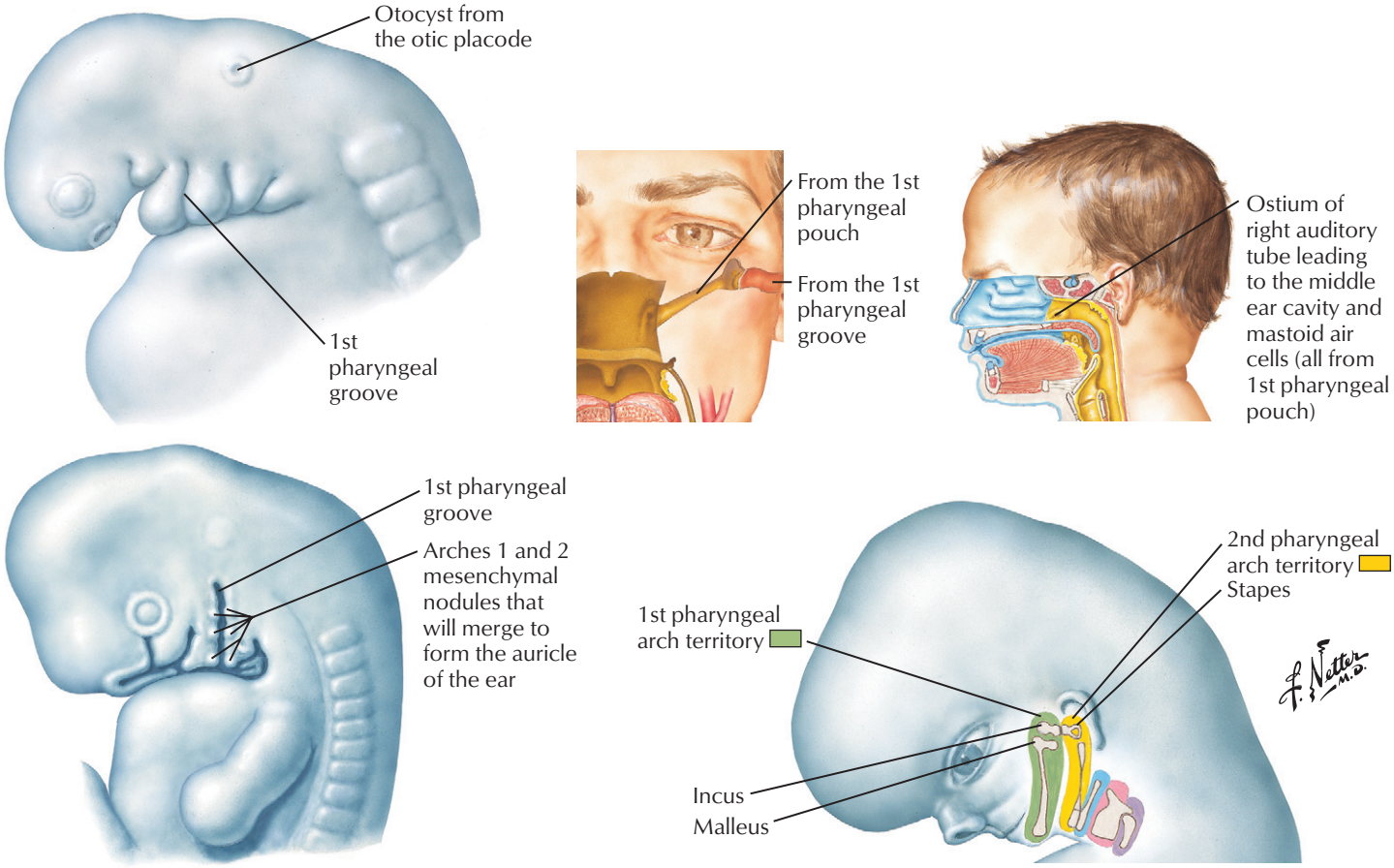


FIGURE 9.20 ADULT EAR ORGANIZATION

The inner ear is a **membranous labyrinth** of sacs (utricle and saccule) and ducts (cochlea and semicircular ducts) housed within a **bony labyrinth,** which is the space in the petrous part of the temporal bone consisting of the cochlear and semicircular canals and vestibule. The membranous labyrinth contains a fluid called **endolymph** and is surrounded by **perilymph** in the **scala vestibuli** and **scala tympani** on either side of the cochlear duct within the cochlear canal.

Primordia of the outer, middle, and inner ear

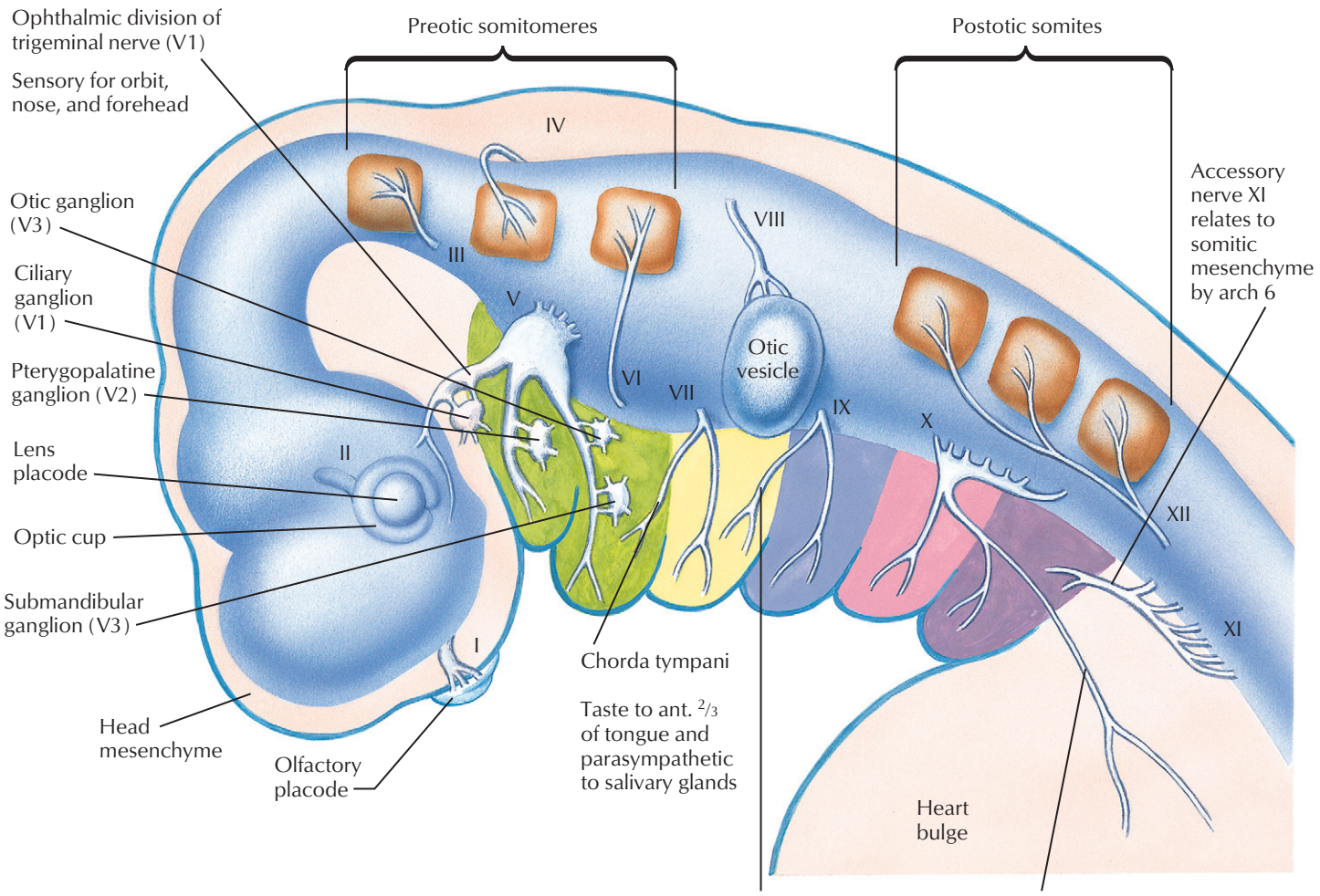


EAR STRUCTURES AND THEIR PRIMORDIA

Structures	Primordia
Auricle	Mesenchyme of the 1st and 2nd pharyngeal arches
External auditory meatus	1st pharyngeal groove (ectoderm)
Middle ear cavity; auditory tube, mastoid air cells	1st pharyngeal pouch (endoderm)
Cochlea and vestibular apparatus	Otic placode/otocyst (ectoderm)
Tympanic membrane	1st pharyngeal membrane (ectoderm/endoderm) with intervening mesenchyme
Ear ossicles	1st pharyngeal arch cartilage (incus and malleus) 2nd pharyngeal arch cartilage (stapes)
Temporal bone	Occipital sclerotomes (mastoid and petrous parts) 2nd pharyngeal arch cartilage (styloid process) 1st pharyngeal arch mesenchyme (squamous and tympanic parts)

FIGURE 9.21 SUMMARY OF EAR DEVELOPMENT

Structures of the external, middle, and inner ear develop from the first and second pharyngeal arches and the groove and pouch between them. Cranial nerve VIII (vestibulocochlear) relates to the otic placode and vesicle and provides the special sensations of hearing and balance. The mandibular nerve (V3 from arch 1) supplies the tensor tympani muscle that dampens the malleus, and the facial nerve (arch 2) supplies the stapedius muscle. Not so obvious is the innervation of the external acoustic meatus and middle ear. General sensation for the former is by the vagus nerve, its only cutaneous branch. Visceral sensation for the middle ear is by the tympanic branch of the glossopharyngeal nerve, the pretrematic branch of IX that is out of its territory (arch 3).



Pharyngeal arches and their nerves:

- Arch 1—trigeminal nerve (V)
  Maxillary part of arch 1—maxillary nerve (trigeminal, V2)
  Mandibular part of arch 1—mandibular nerve (trigeminal, V3)
  Pretrematic branch—ophthalmic nerve (trigeminal, V1)
- Arch 2—facial nerve (VII)
  Pretrematic branch—chorda tympani
- Arch 3—glossopharyngeal nerve (IX)
  Pretrematic branch—tympanic nerve
- Arch 4—vagus n. (X)
- Arch 6—vagus n. (X)

Somite primordia and their nerves:

Preotic somitomeres—oculomotor nerve (III)
trochlear nerve (IV)
abducens nerve (VI)
Postotic somites—hypoglossal nerve (XII)
Somitic mesenchyme—accessory nerve (XI)

Ectodermal structures and their nerves:

Olfactory placode—olfactory nerve (I)
Optic cup—optic nerve (II)
Otic placode—vestibulocochlear nerve (VIII)

FIGURE 9.22 CRANIAL NERVE PRIMORDIA

The 12 pairs of cranial nerves exit the developing brain in sequence, with the exception of the accessory nerve (XI). The nerves relate to surface placodes, the optic cup, head somites, or the pharyngeal arches and innervate all of the structures and tissues that derive from them. The vagus nerve supplies both arches 4 and 6 (the latter branch was formerly considered the "cranial root" of XI). The origin of the mesoderm relating to the accessory nerve (formerly the "spinal root" of XI) is difficult to determine. Because it gives rise to muscle, it must be of somitic origin. It is in the vicinity of the sixth pharyngeal arch, but the trapezius and sternocleidomastoid muscles are otherwise unrelated to the laryngeal and pharyngeal structures that develop from arch 6.

SPECIAL SENSORY AND SOMATOMOTOR CRANIAL NERVE COMPONENTS

Nerve	Primordium Innervated	Neuron Components
Olfactory (I)	Olfactory placode	Special sensory (olfaction)
Optic (II)	Optic cup	Special sensory (vision)
Vestibulocochlear (VIII)	Otic placode	Special sensory (hearing and balance)
Oculomotor (III)	Preotic somitomere	Somatomotor to extraocular eye muscles Parasympathetics to ciliary ganglion (for pupil constrictor and ciliary muscle)
Trochlear (IV)	Preotic somitomere	Somatomotor to superior oblique muscle
Abducens (VI)	Preotic somitomere	Somatomotor to lateral rectus muscle
Hypoglossal (XII)	Postotic somites	Somatomotor to tongue muscles
Accessory (XI)	Somitic mesenchyme by arch 6	Somatomotor to sternocleidomastoid and trapezius

PHARYNGEAL ARCH CRANIAL NERVE COMPONENTS

Nerve	Arch	Neuron Components
Trigeminal (V)	1	General sensory (face, orbit, nasal, and oral cavities) Branchiomotor (muscles of mastication; tensor tympani; tensor veli palatini)
Facial (VII)	2	Branchiomotor (muscles of facial expression; stylohyoid; posterior digastric; stapedius) Special sensory (taste to anterior two-thirds of tongue) Parasympathetic to pterygopalatine and submandibular ganglia (for lacrimal gland, nasal mucosa, and salivary glands)
Glossopharyngeal (IX)	3	Visceral sensory to pharynx Branchiomotor to stylopharyngeus Parasympathetic to otic ganglion (for the parotid gland) Special sensory (taste to posterior tongue; carotid body and sinus)
Vagus (X)	4 and 6	Branchiomotor (pharynx and larynx) Visceral sensory (larynx; foregut below pharynx and midgut) General sensory to external acoustic meatus Parasympathetics (enteric ganglia of foregut and midgut) Special sensory (taste in laryngopharynx; carotid body and sinus)

FIGURE 9.23 CRANIAL NERVE NEURON COMPONENTS

The pharyngeal arch nerves are the territorial nerves of the head and neck with more than one neuron type. Most have branchiomotor neurons for skeletal muscles derived from arch mesenchyme; visceral sensory neurons for the inner, endodermal linings of the arches (pharynx and larynx); and general sensory neurons for surface ectoderm or lining of the stomodeum. The somites give rise to extraocular eye and tongue muscles, and the placodes and optic cup relate to the special sensory organs of the head. Cranial nerves III, VII, IX, and X also exit the brain with presynaptic parasympathetic neurons that are mostly destined for structures in territories distant from their nerve of origin.

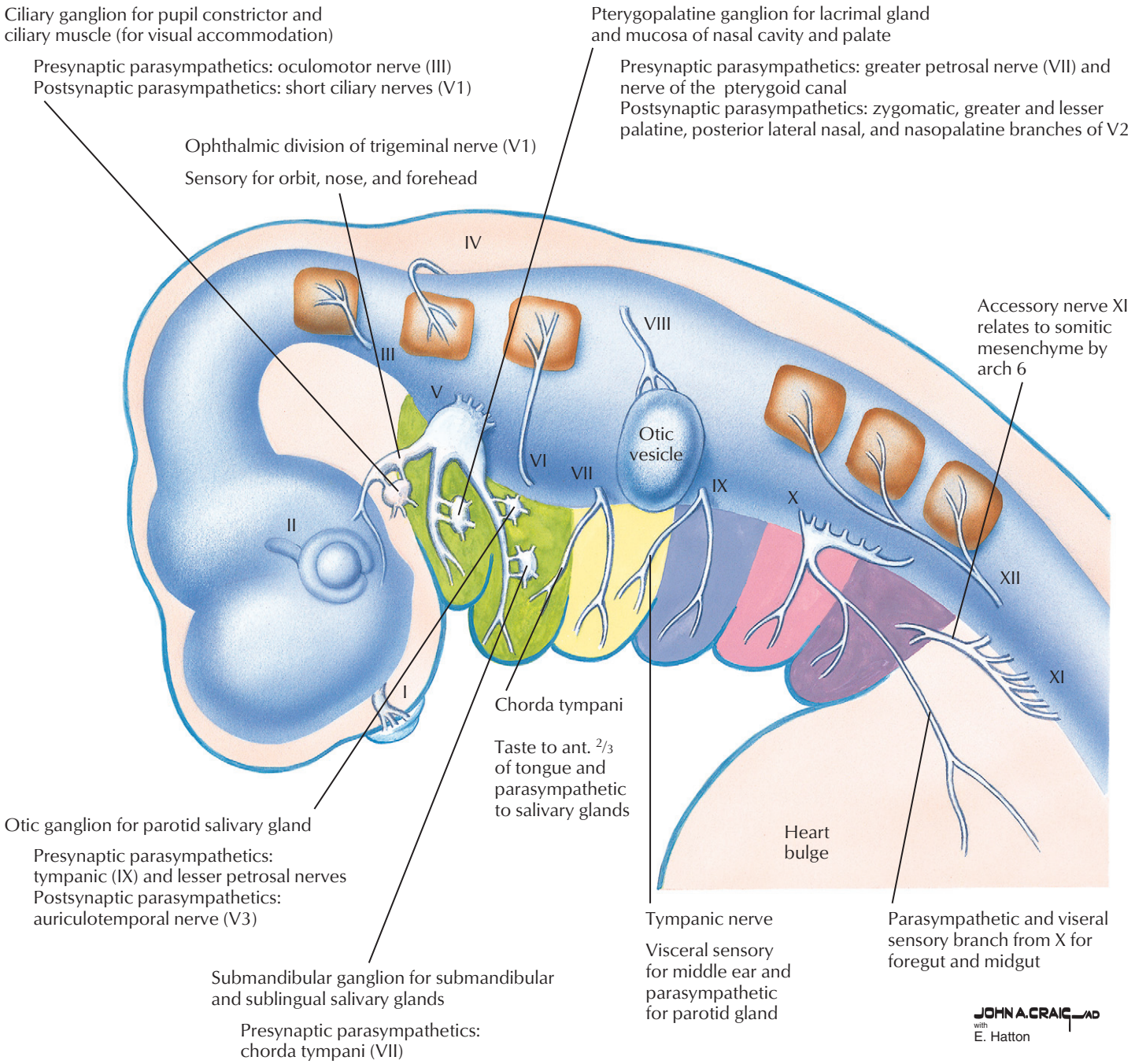


FIGURE 9.24 PARASYMPATHETIC INNERVATION AND UNIQUE NERVES

Presynaptic parasympathetic neurons exit the brain with the cranial nerves III, VII, IX, and X, but all structures in the head that need parasympathetic innervation are in the territory of the trigeminal nerve. Parasympathetics from cranial nerves III, VII, and IX synapse in one of four ganglia, then travel with trigeminal branches to their targets. The **accessory nerve** (XI) is unique. It exits the spinal cord in line with branchiomotor roots of cranial nerves, enters the skull through the foramen magnum, and then exits the skull via the jugular canal to innervate neck muscles. **Pretrematic nerve concept:** The first three pharyngeal arch nerves have branches that leave their arch of origin to provide sensory innervation to the territory immediately preceding its arch.

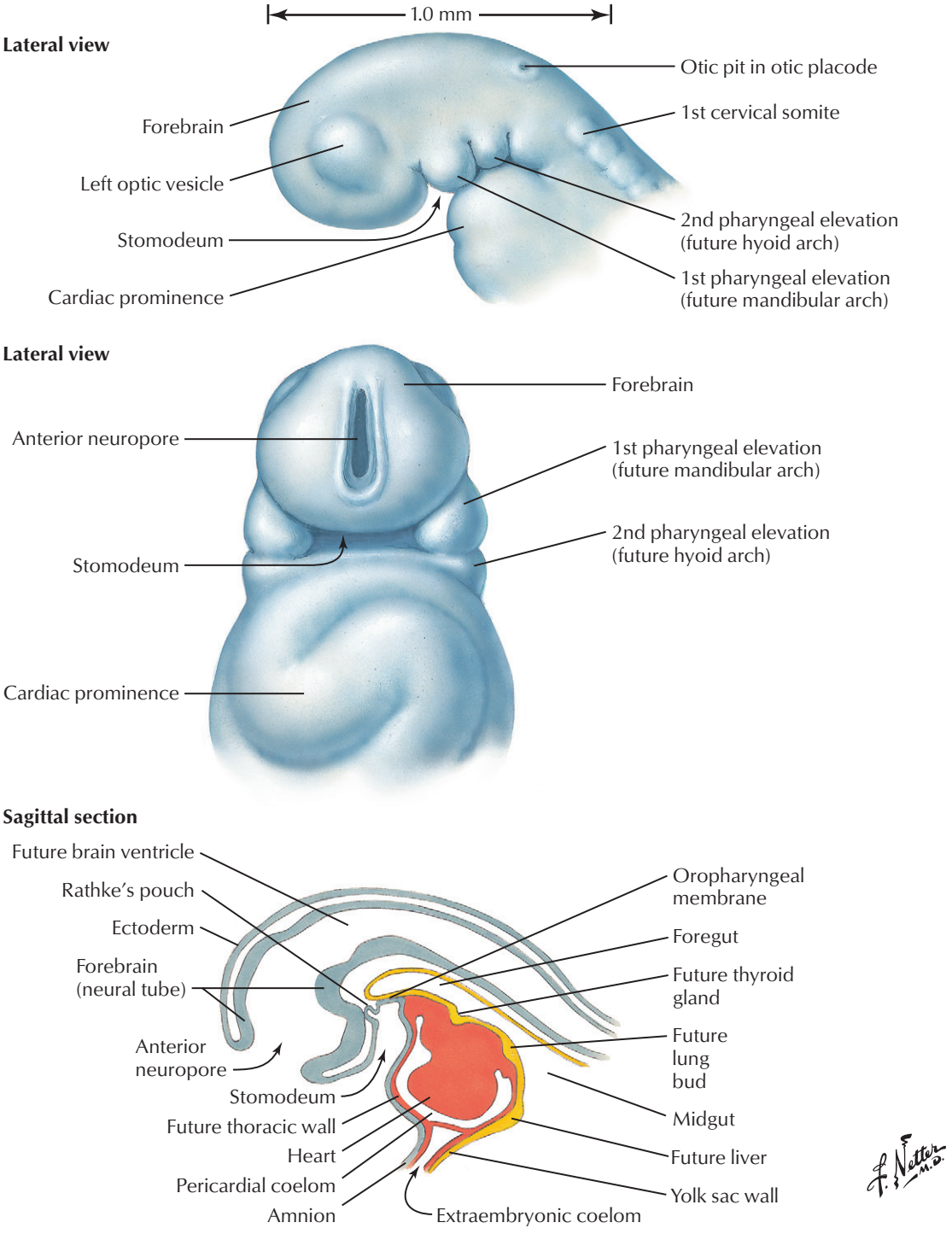


FIGURE 9.25 DEVELOPMENT OF THE FACE: 3 TO 4 WEEKS

The face and head at weeks 3 to 4 are dominated by the appearance of the pharyngeal arches and the invagination of surface ectoderm between relatively huge forebrain and cardiac prominence. This ectodermal recess is the stomodeum, the primitive oral cavity. The otic placode of surface ectoderm is beginning to invaginate to form the otocyst. The lens and nasal placodes are soon to appear. The bulging optic vesicle is the beginning of the formation of the optic cup of neural ectoderm.

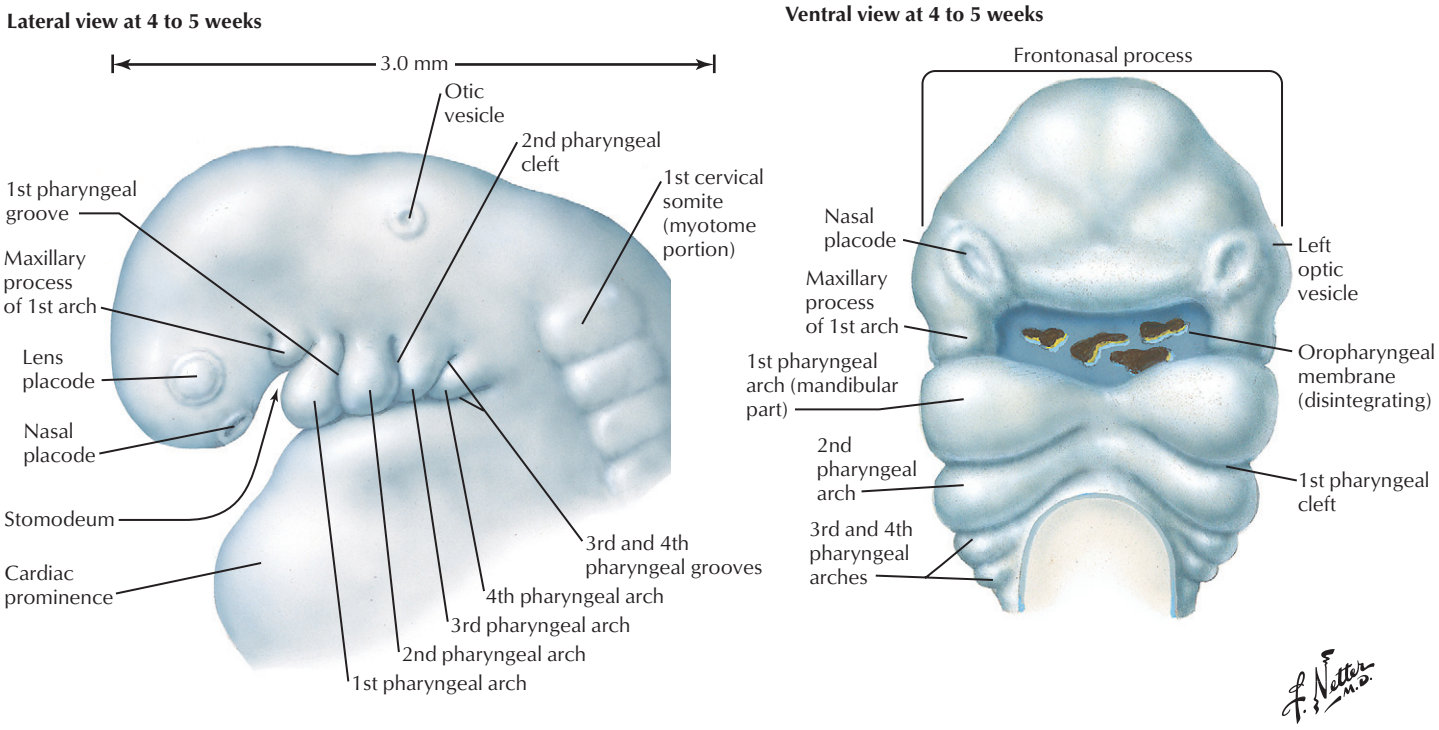


FIGURE 9.26 DEVELOPMENT OF THE FACE: 4 TO 6 WEEKS

By week 4, the mesenchyme around the swelling of the forebrain cranial to the first pharyngeal arch forms a **frontonasal process** that includes the nasal placodes. As the nasal placodes invaginate, **medial and lateral nasal swellings** of mesenchyme form on either side of what are now **nasal pits** or **sacs** in the frontonasal process. The cleft between the lateral nasal prominence of the frontonasal process and the maxillary part of the first pharyngeal arch is the **nasolacrimal groove.** It extends from the medial corner of the developing eye to part of the future nasal cavity and pinches off below the surface to form the **nasolacrimal duct** that drains lacrimal gland secretions (tears) into the inferior meatus of the nasal cavity.

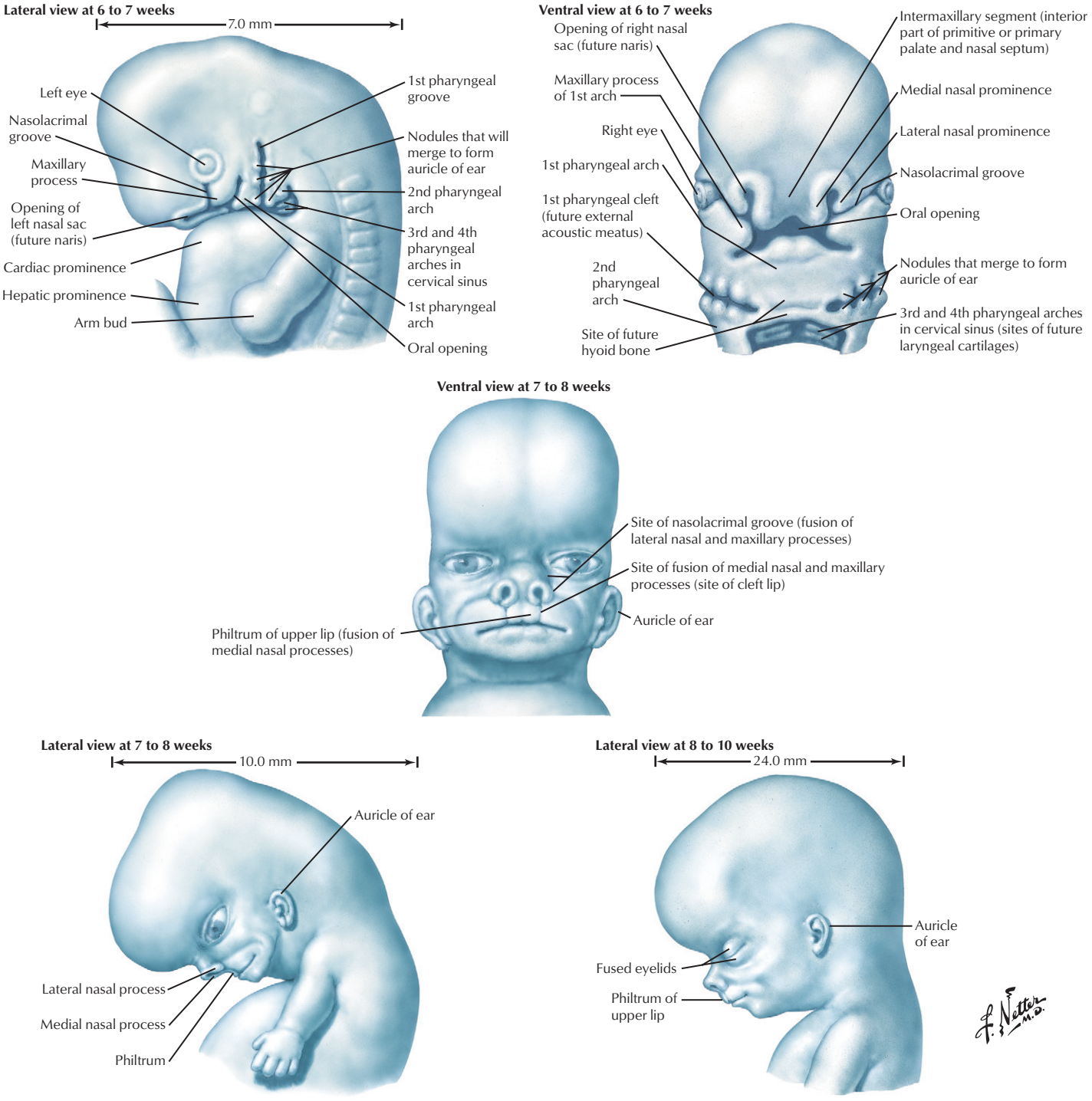


FIGURE 9.27 DEVELOPMENT OF THE FACE: 6 TO 10 WEEKS

The **intermaxillary segment** formed by fusion of the **medial nasal processes** is named for its position between the maxillary processes of the first pharyngeal arch (with which it fuses). It gives rise to most of the external nose, the **philtrum** of the upper lip, and the **primary palate.** The ophthalmic division of the trigeminal nerve (V1), the nerve of the frontonasal process, provides general sensory innervation for all of these midline structures as well as the forehead and orbit. The maxillary nerve (V2) supplies the midface, including most of the maxilla, nasal cavity, and roof of the oral cavity. The mandibular nerve (V3) innervates the mandible and overlying skin in addition to the floor of the oral cavity proper and vestibule.

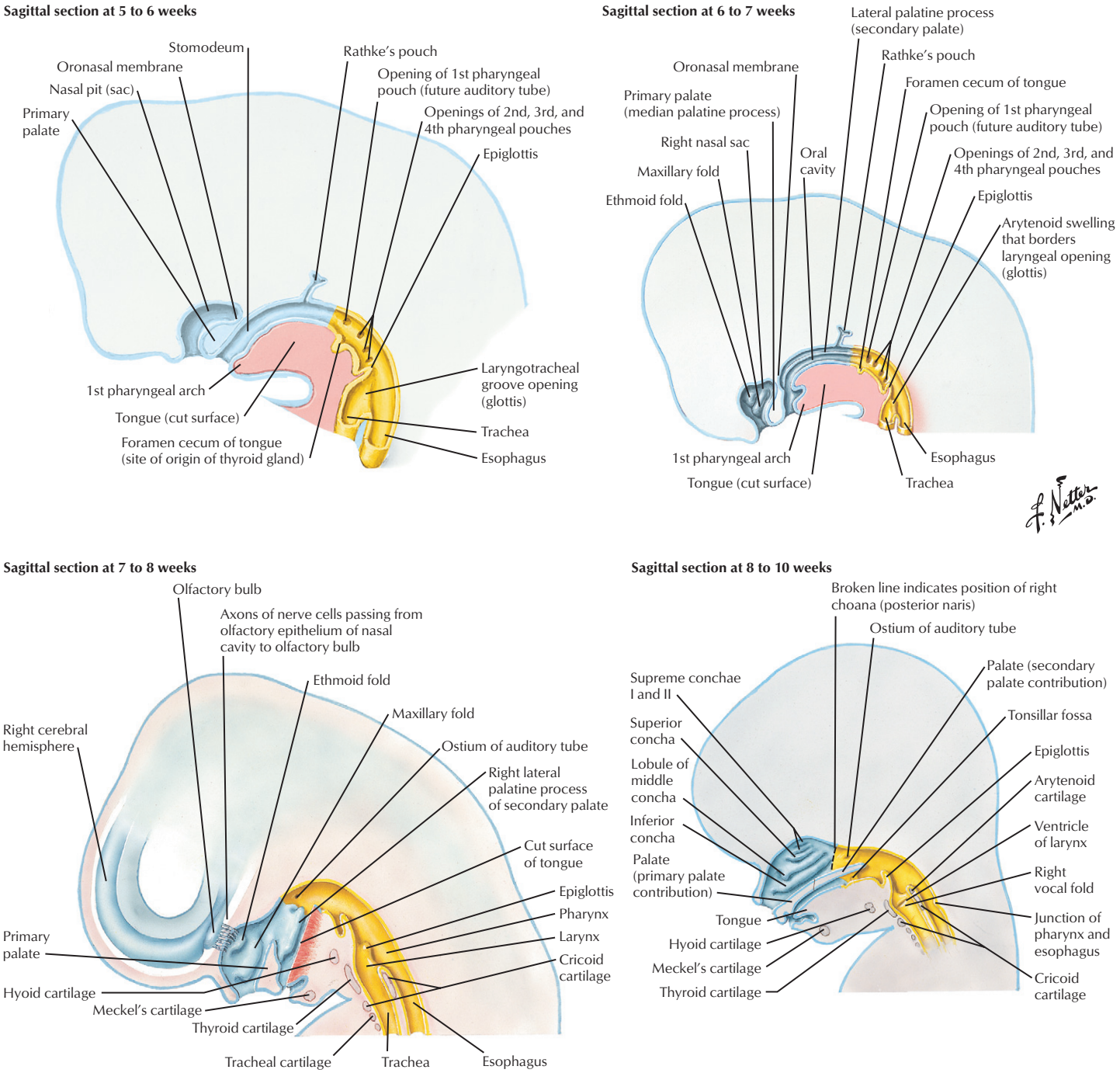


FIGURE 9.28 PALATE FORMATION

At weeks 5 to 6, the nasal sacs are separated from the stomodeum by a thin **oronasal membrane.** The block of tissue between the nasal sacs and stomodeum is the **primary palate. Lateral palatine processes** begin to grow from the maxillary part of the first pharyngeal arch to form the future **secondary palate** posterior to the primary palate. The nasal cavity is derived from the nasal sacs and the posterior portion of the stomodeum above the lateral palatine processes. The **nasal septum** grows inferiorly in the midline. The lateral palatine processes fuse with the nasal septum, and the primary palate fuses with the secondary palate to complete palate formation.

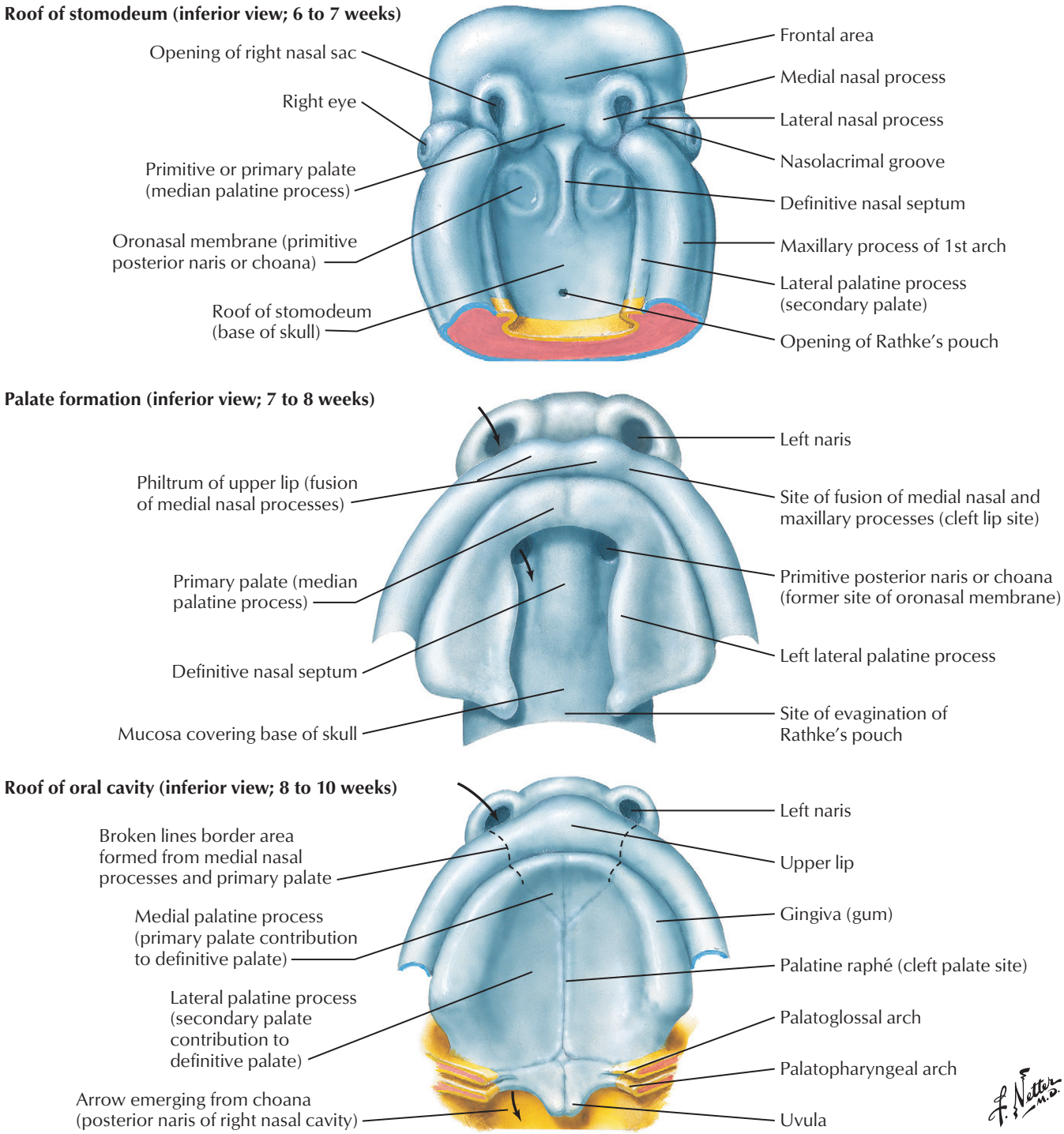
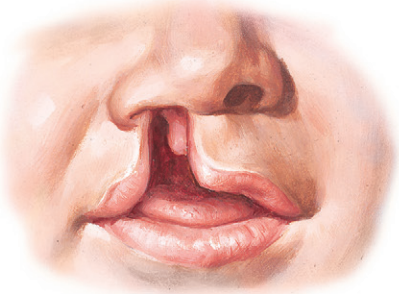


FIGURE 9.29 INFERIOR VIEW OF PALATE FORMATION; ROOF OF THE ORAL CAVITY

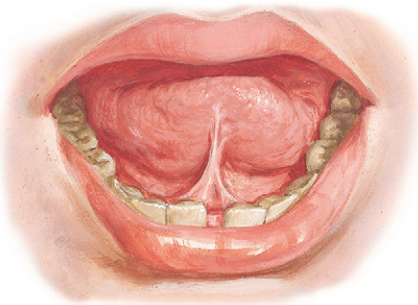
The oronasal membranes break down, and the nasal sacs communicate with the stomodeum. The medial nasal processes of the frontonasal process fuse to form an intermaxillary segment that develops into the philtrum (middle portion) of the upper lip and primary palate. The primary palate gives rise to the **premaxillary ossification center** of the maxilla containing the maxillary incisor teeth. The latter palatine processes form the secondary palate that gives rise to the palatine bones, soft palate, and the rest of the rest of the maxilla.

Unilateral cleft lip—partial

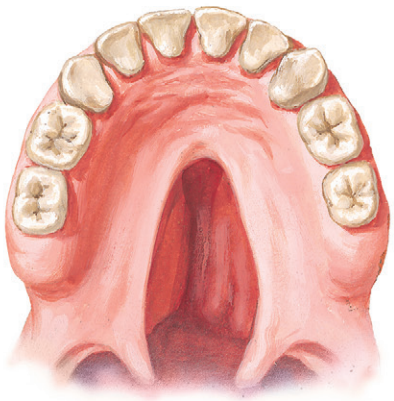


Unilateral cleft of primary palate—complete, involving lip and alveolar ridge

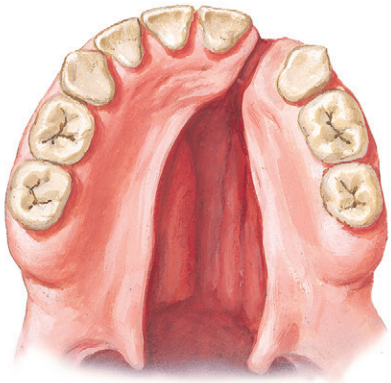
Bilateral cleft lip



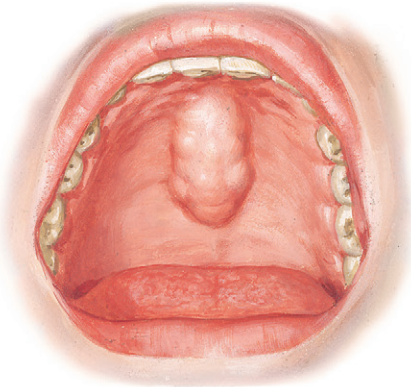
Ankyloglossia—restricted tongue movement from a short lingual frenulum



Partial cleft of palate



Complete cleft of secondary palate and unilateral cleft of primary palate



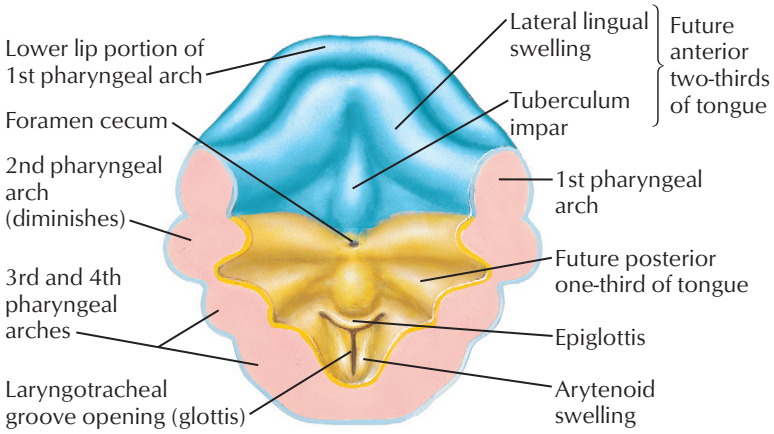
Torus palatinus—bone deposition on palate

F. Netter M.D.

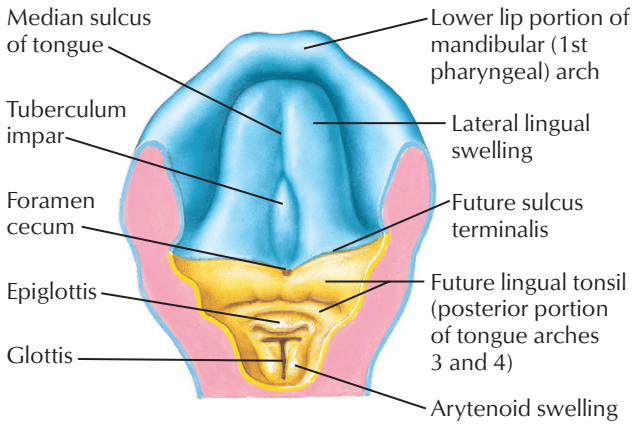
FIGURE 9.30 CONGENITAL ANOMALIES OF THE ORAL CAVITY

Clefts can occur at any point along the site of fusion of the intermaxillary segment of the frontonasal process and the lateral palatine processes. They are classified as anterior or posterior according to their relationships to the incisive foramen located between the primary and secondary palates. Anterior clefts can involve the lip, the alveolar process of the maxilla, or the entire primary palate, and they can be unilateral or bilateral. Posterior clefts may affect just the soft palate or the soft and posterior bony palate (secondary palate). These are midline clefts, and the nasal septum may be fused to the hard palate on one side or not at all. Anterior and posterior clefts are unrelated; they have different frequencies and population occurrences.

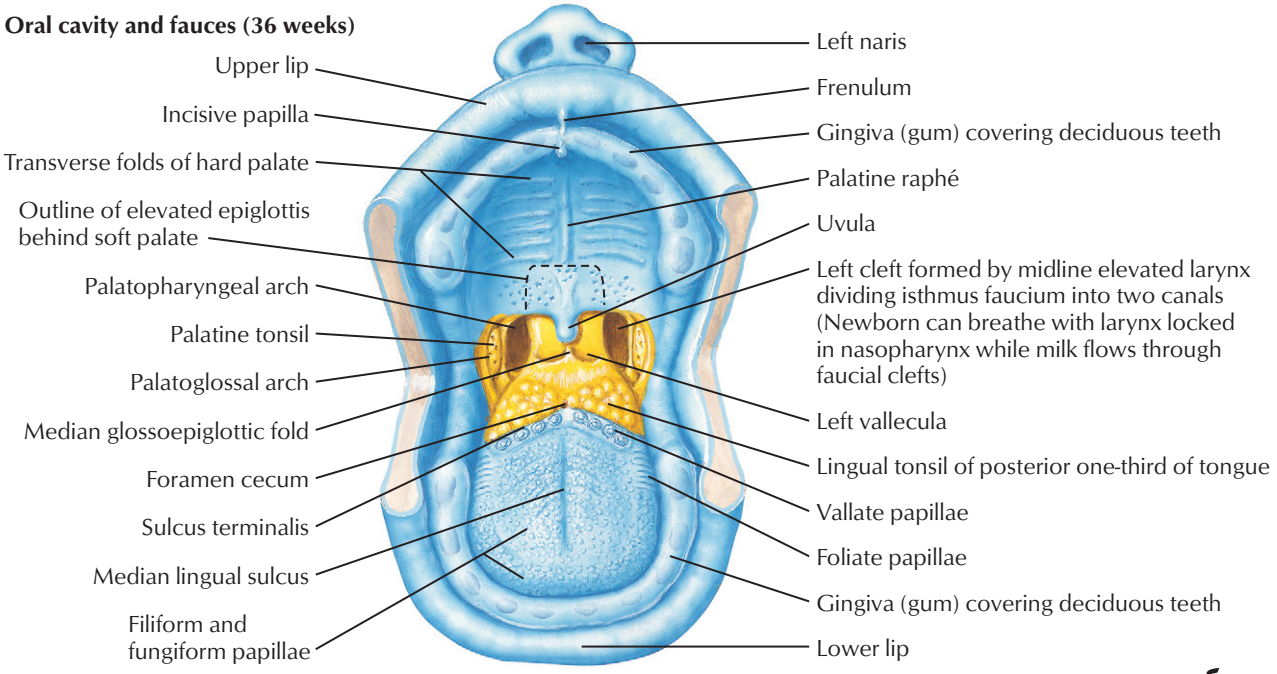
Floor of oral cavity and pharynx (superior view; 5 to 6 weeks)



Floor of oral cavity and pharynx (superior view; 6 to 7 weeks)



Oral cavity and fauces (36 weeks)



Ectodermal lining
Endoderm lining

INNERVATION OF THE TONGUE

Anterior two-thirds (oral cavity)	General sensory (GSA)—lingual branch of V_3 Taste (SVA)—facial nerve (VII)
Posterior one-third (oropharynx)	Visceral sensory (GVA) — glossopharyngeal nerve (IX) Taste (SVA) — glossopharyngeal nerve (IX)
Root (laryngopharynx)	Visceral sensory (GVA) — vagus nerve (X) Taste (SVA) — vagus nerve (X)
Tongue muscles	Somatomotor — hypoglossal nerve (XII)

FIGURE 9.31 FLOOR OF THE ORAL CAVITY

The ectoderm of the oral cavity receives a very rich general sensation; the foregut is supplied with less intense visceral sensation, with the degree of sensation diminishing from pharynx to esophagus. Because the lining of arch 2 does not grow much, the facial nerve does not contribute to the general or visceral sensation of the tongue.

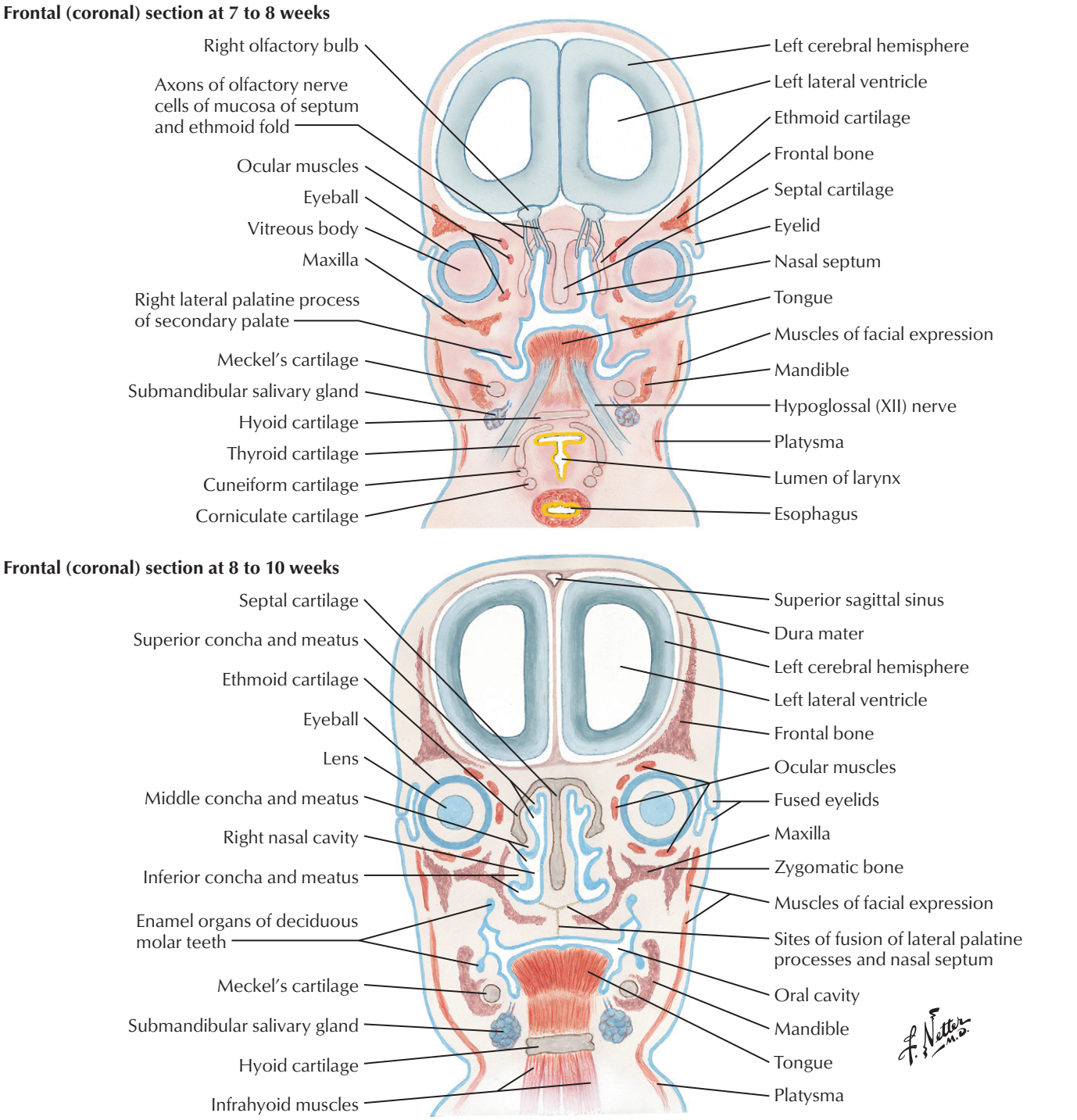


FIGURE 9.32 DEVELOPMENTAL CORONAL SECTIONS

Although thin in the adult, the nasal septum in the embryo is thick and is a driving force in the vertical growth of the head. The lateral palatine processes (secondary palate) are angled inferiorly when they first develop. The tongue must drop down before they can swing up toward the nasal septum. The eyes face laterally on the embryonic head. The eyelids fuse in the early fetus (8 to 10 weeks), and then reopen by week 26.

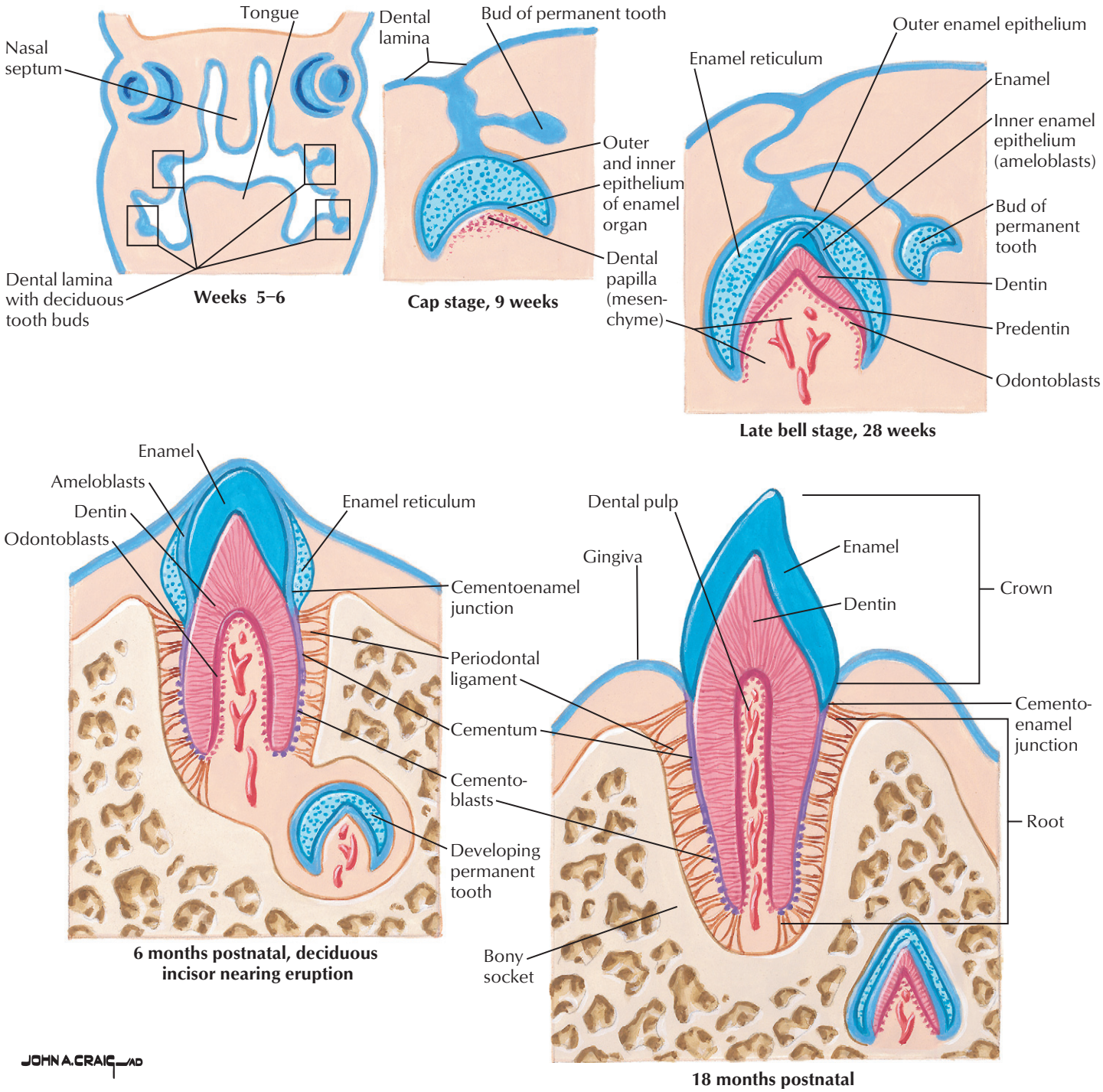
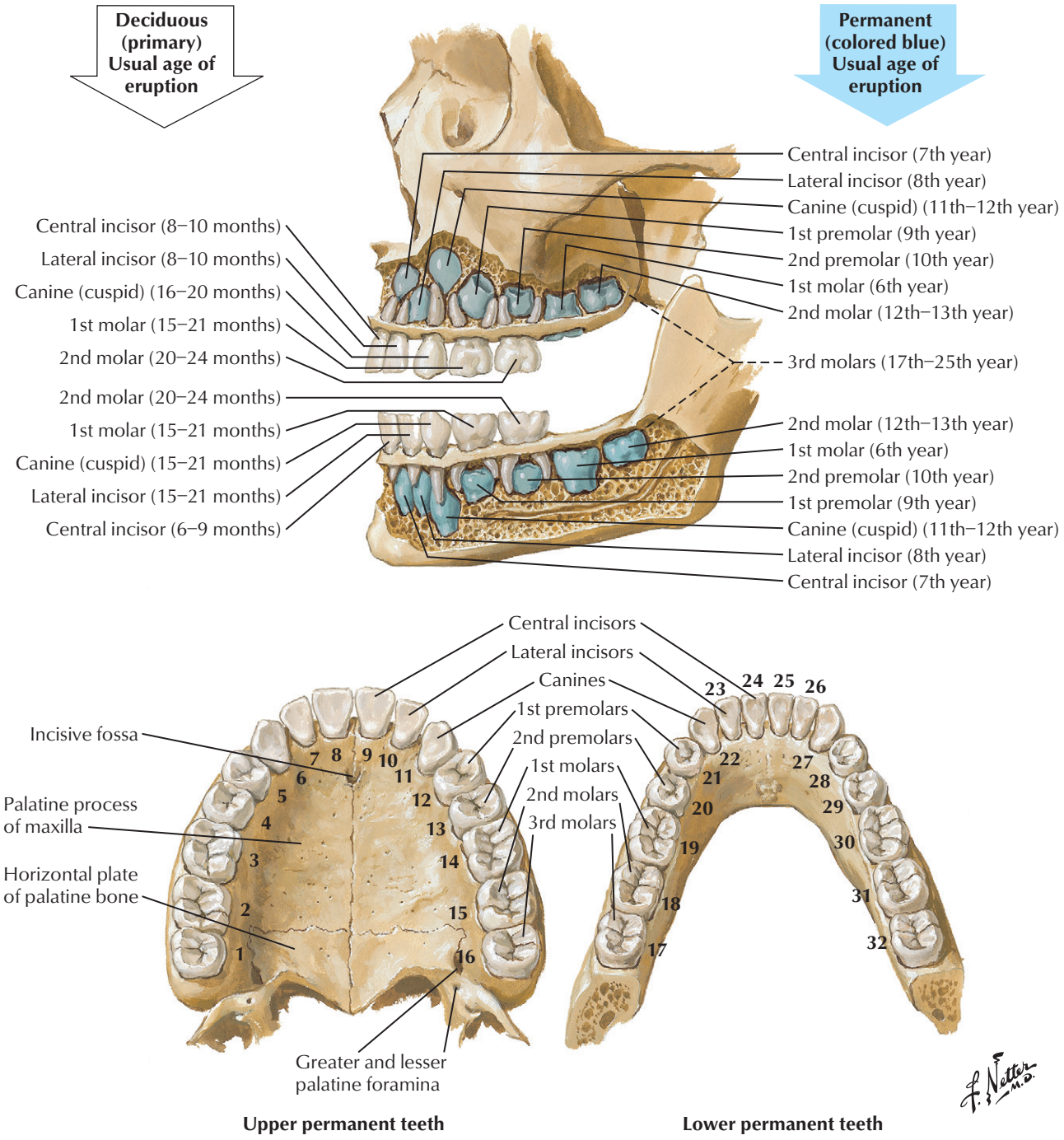


FIGURE 9.33 TOOTH STRUCTURE AND DEVELOPMENT

In week 6, the oral ectoderm thickens to form U-shaped **dental laminae** in the upper and lower jaws. Extensions of the dental lamina give rise to epithelial **enamel organs** that surround mesenchymal **dental papillae** to form tooth buds by week 9. Enamel and dentin are secreted at the interface of the two primordia. The enamel-forming **ameloblasts** are on the inner layer of an enamel organ, and the outer mesenchymal cells of a dental papilla form an epithelial layer of **odontoblasts** that secrete dentin. Tooth formation involves a complicated series of inductive events between epithelium and mesenchyme (in both directions), with at least eight signaling molecules. The ectodermal epithelium initiates the cascade, and the mesenchyme determines whether a tooth becomes an incisor or molar.



Note: Numbers refer to a common scheme dentists use to identify teeth. (Letters are used for the deciduous dentition.)

FIGURE 9.34 DENTAL ERUPTION

The crowns of the teeth are completely formed in the jaws before they erupt. Space constraints inhibit root development, which is completed during eruption of the tooth. Because enamel is acellular, no growth of a crown is possible after eruption. The deciduous (primary or "baby") teeth fall out when their roots are resorbed as a result of development and eruption of the permanent crowns.

Terminology

Ankyloglossia	(G., "crooked tongue") Restricted mobility of the tongue caused by a short lingual frenulum, a frenulum attached too close to the tip of the tongue, or fusion of the tongue to the floor of the oral cavity.
Ansa cervicalis	(ansa, L., "handle") Nerve loop of the cervical plexus lying on the carotid sheath. It is motor to the infrahyoid strap muscles.
Branchial	(G., referring to "gills") Pharyngeal arches used to be called branchial arches in reference to the phylogenetic origin of the arches as the gill apparatus in fish. In higher animals, they flank the pharynx and become a variety of structures.
Branchiomotor	Classification of motor neurons to striated muscle derived from the pharyngeal arches. They differ from somatomotor neurons according to muscle primordia only.
Cervical sinus	Ectodermal invagination formed by the merging of pharyngeal grooves 2, 3, and 4. It disappears, and the ectoderm of arches 2 through 6 contributes to little in the adult.
Foramen cecum	Blind pit on the back of the tongue that is the site of the endodermal thyroid diverticulum that descends to its final location anterior to the trachea.
Hyoid arch	The second pharyngeal arch.
Hyomandibular cleft	The first pharyngeal groove between the mandibular part of the first pharyngeal arch and the second (hyoid) pharyngeal arch.
Hypobranchial eminence	Mesenchymal swelling in the third and fourth pharyngeal arches that contributes to the posterior, pharyngeal part of the tongue and the epiglottis.
Meckel's cartilage	The cartilage of the first pharyngeal arch that becomes the malleus, incus, and sphenomandibular ligament. It does not contribute to the mandible, which is mostly membrane bone that condenses around the cartilage.
Nervus intermedius	The sensory (taste) and parasympathetic root of the facial nerve (cranial nerve VII). *Intermedius* refers to its location between the large branchiomotor root of VII and nerve VIII.
Neurocranium	The bones surrounding the brain. The bottom of the neurocranium is the cranial base at the interface between neurocranium and viscerocranium.
Oropharyngeal membrane	Membrane of ectoderm and endoderm in the gastrula that separates the stomodeum (primitive oral cavity) from the foregut (primitive pharynx). It breaks down in the fourth week.
Pharyngeal grooves	Ectodermal clefts between the pharyngeal arches on the surface. They persist as the external auditory meatus only.
Pharyngeal membranes	A membrane of ectoderm, mesoderm, and endoderm where a pharyngeal groove abuts a pharyngeal pouch between the pharyngeal arches. The first persists as the tympanic membrane (eardrum).
Pharyngeal pouches	Endodermal extensions of the foregut between the pharyngeal arches on the inside. They give rise to the auditory tube, middle ear cavity, mastoid air cells, thymus, parathyroid glands, and C cells of the thyroid.
Placode	Thickening of surface ectoderm that relates to special sensory nerves I, II, and VIII. They form olfactory epithelium and nerves, the lens of the eye, and the vestibulocochlear apparatus for balance and hearing.

Terminology, cont'd

Premaxilla	Part of the maxilla; with the incisor teeth, it is derived from the primary palate, a derivative of the frontonasal process. Its ossification center fuses with the rest of the maxilla (from the lateral palatine processes) in humans.
Pretrematic	(trema, L., "slit") In front of the gill slit. Pretrematic nerves provide sensory innervation to the arch or area in front of their arches of origin. They are the ophthalmic division of the trigeminal nerve (V1), the chorda tympani (VII), and the tympanic nerve (IX).
Preotic	Refers to somitomeres in front of (cranial to) the otic placode that give rise to extraocular eye muscles. Postotic somites (or somitomeres) for tongue muscles are behind (caudal to) the otic placode.
Spinal accessory nerve	Traditionally considered the 11th cranial nerve with a cranial root accessory to the vagus nerve and a spinal root for the trapezius and sternocleidomastoid muscles. More recently thought that the cranial root has no connection to the spinal root and is part of the vagus nerve. The spinal root is the entire accessory nerve and is unique; it is not a cranial nerve and exits the spinal cord in a different location than cervical spinal nerves.
Stomodeum	Invagination of surface ectoderm that forms the primitive oral cavity and posterior part of the primitive nasal cavity.
Synostosis	The closure or ossification of sutures by the replacement of the fibrous connective tissue with bone.
Thyroglossal duct	An elongation of the thyroid diverticulum formed as the thyroid primordium descends from the back of the tongue to the front of the trachea. Initially, it has a lumen that may persist as a sinus or cyst in the tongue.
Tuberculum impar	A mesenchymal swelling on the floor of the stomodeum that, together with lateral lingual swellings of the first pharyngeal arch, forms the basis of the anterior two-thirds of the tongue.
Ultimobranchial body	An antiquated, cryptic term for the ultimate or last extension off the fourth pharyngeal pouch that develops into the calcitonin-producing parafollicular cells (C cells) of the thyroid gland. Also called the postbranchial body.

Neuron Terminology

Traditional Neuron Terminology	Terms Used in This Book
General somatic afferent (GSA)	General sensory
General somatic efferent (GSE)	Somatomotor
General visceral afferent (GVA)	Visceral sensory
General visceral efferent (GVE)	Parasympathetic
Special visceral efferent (SVE)	Branchiomotor
Special somatic afferent (SSA) (vision, hearing)	Special sensory
Special visceral afferent (SVA) (taste, smell)	Special sensory

SUMMARY OF COMMON CONGENITAL ANOMALIES THROUGHOUT THE BODY AND THEIR EMBRYONIC CAUSES

CONDITION	EMBRYOLOGICAL BASIS
Anencephaly	Absence of part of the brain from a neurulation defect where the neural tube does not close and the overlying skull is not able to form. It is the head equivalent of spinda bifida with myelocele.
Anular pancreas	A pancreatic head that encircles the duodenum when the ventral pancreatic bud improperly migrates around both sides of the abdominal foregut tube to fuse with the dorsal pancreatic bud and trails pancreatic tissue along its bifid path.
Bladder-rectum fistula	Improper division of the hindgut cloaca into the rectum and urogenital sinus (bladder, urethra, and related glands).
Bicornuate uterus	Bifid uterus ("two horns") that develops from the left and right paramesonephric (müllerian) ducts in addition to the fused uterovaginal primordium. Other abnormalities of the uterus and/or vagina result from improper development of the uterovaginal primordium and/or one or both of the ducts.
Cleft lip/primary palate	Failure of the lower part of the frontonasal process (intermaxillary segment with its median palatine process) to fuse with the maxillary part of the first pharyngeal arch. It can be unilateral or bilateral.
Cleft secondary palate	Failure of the lateral palatine processes of the maxillary part of the first pharyngeal arch to fuse with each other and/or the nasal septum.
Coloboma of the eye	Failure of closure of the ventral cleft in the optic cup. Can result in anything from a small defect in the iris to large gaps in the iris, ciliary body, and/or retina.
Cryptorchidism	Undescended testes in the abdominal cavity or inguinal canal. Sterility results if both testes are undescended.
Detached retina	The two layers of the optic cup never tightly fuse, and the inner layer (visual retina) can fall away from the outer layer (pigmented retina).
Diaphragmatic hernia	Most often a failure of the pleuroperitoneal membranes to close off the central tendon of the diaphragm to complete the separation of the pleural and peritoneal coelomic cavities.
DiGeorge syndrome	Absence of the thymus and parathyroid gland from defective development of the third and fourth pharyngeal pouches. Results in immune deficiency from defective T-cell function. Often accompanied by first arch defects of the face and ears.
Double aortic arch	Persistence of the proximal part of the right dorsal aorta to form a vascular sling around the trachea and esophagus. The aorta and the superior and inferior vena cavae are initially paired vessels that may persist.
Ectopia cordis	A gastroschisis-type defect of the thorax where the heart extends outside the thoracic wall.

Condition	Embryological Basis
Ectopic parathyroids	Typically, these are the inferior parathyroid glands from pharyngeal pouch III. They descend with the thymus gland, sometimes all the way into the mediastinum. The superior parathyroid glands are from pouch IV and do not migrate very far to their adult location behind the thyroid gland.
Ectopic thyroid tissue	Located anywhere along of the path of the thyroglossal duct: from the tongue to the trachea anterior to the hyoid bone and larynx. There can also be cysts in a patent duct. The foramen cecum on the tongue is the site of the thyroid diverticulum.
Ectopic ureters	The metanephric ducts (ureters) can open in many locations in the bladder and other organs. They originate from the caudal end of the mesonephric duct and are often "carried" with it to a lower position than normal (e.g., urethra), particularly in the male.
Epispadius	A penile urethra that opens on the dorsal surface of the penis due to improper location of the phallic tubercle relative to the urogenital sinus.
Exstrophy of the bladder	A gastroschisis-type defect of the lower abdominal wall where the bladder extends outside the abdominal wall.
External auditory meatus atresia	Failure of the cellular plug in the meatus (developing from the first pharyngeal groove) to canalize. Often related to first pharyngeal arch syndrome, in which neural crest cells fail to migrate into the arch in sufficient numbers.
Gartner's duct cyst	A remnant of the male duct primordium (the mesonephric or wolffian duct) in the broad ligament of the uterus.
Gastroschisis	An abdominal hernia through a body wall defect resulting from incomplete folding of the gastrula or ventral muscle migration. It can look like an omphalocele, but the intestines do not extend into the umbilical cord (they are usually to the right of the umbilical ring), and the viscera are directly bathed in amniotic fluid. The "split stomach" term is a misnomer.
Hepatic segment of inferior vena cava absent	The vitelline veins fail to form the hepatic segment of the inferior vena cava. Blood from the lower inferior vena cava reaches the heart via the azygous vein.
Holoprosencephaly	The most severe consequence of fetal alcohol syndrome, it is the failure of midline cleavage of the embryonic forebrain. Numerous abnormalities may include a small forebrain, a single ventricle, absence of olfactory bulbs and tracts (arrhinencephaly), and facial deformities (e.g., eyes close together).
Horseshoe kidney	The left and right metanephric kidneys, with their ureteric buds, fuse in the midline of the pelvis and hook around the inferior mesenteric artery as they ascend.
Hydrocephaly	Excess cerebrospinal fluid (CSF) that dilates the ventricles or accumulates around the brain. Results from blockage within the ventricular system (obstructive hydrocephaly, e.g., aqueductal stenosis or atresia of the foramina of Luschka and Magendie) or in the flow of CSF in the subarachnoid space (communicating hydrocephaly).
Hypospadias	A penile urethra that opens on the ventral surface of the penis. The urogenital (UG) folds fail to enclose the distal part of the UG sinus on the ventral surface of the phallic tubercle (developing penis). The UG endoderm normally connects to an invagination of ectoderm from the tip of the glans penis to complete penile urethra development.

Condition	Embryological Basis
Indirect (congenital) hernia	A patent processus vaginalis (a finger-like extension of parietal peritoneum through the inguinal canal that typically closes) is a ready-made hernial sac. Its partial closure can result in cysts.
Interatrial septal defect	The embryonic single atrium is divided into left and right chambers by a septum primum with a foramen secundum and a septum secundum with a foramen ovale. A septal defect usually results when one or both foramina are too large and they overlap too much.
Interventricular septal defect	The embryonic interventricular septum (which becomes the muscular IV septum) fails to fuse properly with the endocardial cushions and the spiral (aorticopulmonary) septum. This fusion defect is in the upper membranous part of the IV septum. Holes can also develop within the muscular IV septum.
Meckel's diverticulum	Remnant of the yolk sac stalk extending from the midgut (ileum). Its inflammation can mimic the pain of appendicitis. The stalk can also be a cyst or fistula.
Megacolon	Lack of peristalsis due to the failure of neural crest cells to migrate into the colon and differentiate into neurons of the enteric nervous system in the smooth muscle wall of the colon.
Multiple renal vessels	A by-product of the unusual mechanism of kidney blood vessel development. Most organs (e.g., gonads, muscles) trail their blood supply as they migrate. As the kidneys ascend from the pelvis, new vessels develop and connect to them at successively higher levels. The lower ones usually disappear, but may persist as multiple renal vessels from the aorta and/or inferior vena cava.
Nasolacrimal duct defect	A "tear duct" that opens on the surface at the side of the nose. Results from failure of the middle part of the frontonasal process alongside the developing nose to fuse with the maxillary part of the first pharyngeal (branchial) arch. The ectodermal cleft between these swellings normally invaginates to form the duct.
Oligohydramnios	Low amount of amniotic fluid that results in fetal compression and associated deformities (e.g., Potter's syndrome). May be caused by low fluid production from renal agenesis.
Omphalocele	Congenital umbilical hernia. The rapidly growing intestines of the midgut leave the fetal abdominal cavity and enter the umbilical cord as a normal part of development. Sometimes, they fail to return to the abdominal cavity.
Pelvic kidney	Failure of the kidneys to ascend from the pelvis, where the metanephric diverticulum originates from the caudal end of the mesonephric duct.
Pharyngeal (branchial) cysts and sinuses	A persistence of the cervical sinus, which is a fusion of pharyngeal grooves II, III, and IV below the surface. Cysts and internal sinuses can also be remnants of pharyngeal pouches.
Pharyngeal (branchial) fistulas	Communication between the surface of the neck and the lumen of the pharynx (usually at the palatine tonsil) or larynx when a pharyngeal membrane breaks down between an external pharyngeal groove and internal pharyngeal pouch.
Polyhydramnios	Excess amniotic fluid that may result from anencephaly, esophageal atresia, or other anomalies that impair the drinking, swallowing, and/or absorption of amniotic fluid in the fetus.

Condition	Embryological Basis
Respiratory distress syndrome (RDS)	The absence or reduction of surfactant, a detergent produced by type II alveolar cells (pneumocytes) that reduces surface tension to maintain alveolar patency. It results from premature birth (before 6 months) or damage to type II cells.
Scoliosis	Absence of a somite or sclerotome on one side of the embryo. Only half of a vertebra develops, and a congenital lateral bending of the vertebral column (scoliosis) is the result. Postnatal scoliosis is caused by an imbalance in the tone of the intrinsic back muscles on one side compared to the other.
Spina bifida	Neural tube defect. It can remain on the surface (spinal cord exposed) or sink below, but not enough for sclerotome cells to envelop it. All cases have an absent or incomplete vertebral arch over the spinal cord, hence the "bifid spine."
Tethered cord syndrome	A low positioning of the termination of the spinal cord below L1 by the filum terminale that may result from abnormal secondary neurulation. May be associated with sensory and motor symptoms in pelvic organs (e.g., incontinence) and the lower extremities.
Tetralogy of Fallot	An unequal division of the truncus arteriosus by the spiral septum, which leads to four major defects: (1) pulmonary trunk stenosis (narrowing), (2) interventricular septal defect, (3) large aorta overriding the IV defect and draining both ventricles, and (4) hypertrophy of the right ventricular wall.
Transposition of the great vessels	Failure of the spiral (aorticopulmonary) septum to take a spiral path in dividing the truncus arteriosus into the ascending aorta and pulmonary trunk. The aorta drains the right ventricle and the pulmonary trunk, the left ventricle. Pulmonary and systemic circulation are parallel systems, and oxygenated blood does not get to the body tissues. Death at birth results unless there is communication between the systems (e.g., septal defects).
Urachal cyst/sinus/ fistula	The urachus is a remnant of the allantois, the fourth extraembryonic membrane that extends from the bladder into the umbilical cord. A cyst will be inferior to the level of umbilicus. Urine will pass to the surface of the abdomen through a urachal fistula.

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